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POLYGENIC RISK SCORES AND TYPE 2 DIABETES: MODULATION BY OBESITY AND DIETARY INTERVENTION IN DETERMINING DIABETES INCIDENCE AND CARDIOVASCULAR DISEASES

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1. Project Summary

General Summary

Background / Objectives: Type 2 diabetes (DT2) is one of the leading causes of cardiovascular disease (CVD). Although obesity has been identified as a major risk factor for DT2, not all obese individuals develop DT2 and so it is important to discover the genetic factors associated with an increased risk of DT2 in obese people in order to act on them through their environmental modulation. Similarly, the genes associated with DT2 should be identified in non-obese individuals. Therefore, our main goal is to analyze the genetic heterogeneity of the risk of DT2 according to obesity status, and to develop genetic risk scores (GRS) in obese and non-obese individuals. We will also examine the association of these GRS with the incidence of CVD, as well as modulation by the Mediterranean diet (DietMed).

Design and Methods: We will carry out a follow-up study (median 5.7 years) in about 7000 participants of high cardiovascular risk (over 67 +/- 7 years and 48.5% DT2 at the beginning of the study) to analyze the interaction between SNPs associated with DT2 and obesity (46.8% obese at baseline) on the incidence of DT2 to construct obesity-specific GRS (including both new SNPs discovered to be relevant in this project and SNPs previously known from publications). Genome-wide genotyping will be performed in a subsample including the incident cases of DT2 (315) and the corresponding controls (at least two per case). The ROC curves will be used for the selection of the SNPs and GRS with better predictive value both in general and by obesity status. In addition, a list of more than 23 SNPs (the GRS) will be genotyped in all participants and multivariate Cox regression models with interaction terms will be adjusted to calculate the Harzad ratios (HR) and 95% CI. Thus, the risks of DT2 and CVD risks associated with these GRS in the whole population and stratified by obesity status will be estimated. Additional modulation by DietMed will be investigated in multivariate models. To better understand the mechanisms for the associations and modulations, a pilot analysis of epigenome-wide methylation (EWAs) with the EPIC 850K array will be performed in a subsample of DT2 cases and controls and the top-ranked differentially methylated loci will be validated in a larger subsample of cases and controls. Finally, the genetic-epigenetic results (also with the possibility of other omics data) as well as the main exposomic variables will be integrated to have a more complete picture of these interactions in the disease.

Results summary

The project results are very relevant. We have investigated the genetic determinants of diabetes in the whole population, also taking into account the influence of obesity on the Mediterranean subjects at high cardiovascular risk. We used both the genome-wide association study (GWAS) approach and the candidate gene approach, which has been important in other populations. With this we have created genetic risk scores (GRS) associated with the risk of prevalent diabetes, incident diabetes and cardiovascular disease. Each of the GRS created showed specific associations, indicating the importance of taking into account the characteristics of the population (both demographic and geographical) and the phenotype studied when conducting genomic research with possible applications in precision medicine. We found great heterogeneity due to obesity, obtaining a combination of polymorphisms that are associated with diabetes only in obese people, while another combination of polymorphisms is associated with diabetes in non-obese people. We have calculated the predictive value of these GRSs showing that if we apply an obese GRS to non-obese people, the predictive value is almost nil and vice versa. This is very relevant for the applications of genetic testing because until now the starting phenotypic characteristics of the tested person were not considered and in our study we found that they are crucial. We also analyzed the data from a gender perspective and found differences in the predictive values of genetic polymorphisms between men and women, providing more evidence to consider the sex variable relevant in future precision medicine.

2. Results obtained

In the analysis of GWAS in the genome-wide sample, we performed an association study of the genome-wide distributed SNPs (more than 700,000 SNPs) with **prevalent diabetes.** The most significant SNPs detected as top-ranked corresponded to some genes previously identified with those associated with diabetes in different studies. For example, we found as top-ranked, the TCF7L2 gene which is one of the genes most associated with diabetes worldwide. Other SNPs have also been previously associated with diabetes, but the magnitude and frequency vary depending on the population studied. In our case, SNPs in the CUB and Sushi (CSMD1) gene multiple domains 1, was very significant. This gene was reported in a diabetes GWAS in the Hispanic population of Texas (Parra et al., 2011; Diabetology). This illustrates another important

aspect that we have highlighted in some of our publications (Ortega-Azorín et al., 2019, Nutrients). This is due to the fact that SNPs that have been published as the most relevant associated with certain cardiometabolic phenotypes do not have the same effect in all populations. Therefore, the use of GRS created with SNPs derived from analyzes performed in other populations, for example in northern Europe, may not be valid in the Mediterranean population. Therefore, GWAS studies have to be conducted in the specific population in which the predictive value of the associations must be tested. Continuing with the hypothesis of our study, that the genes associated with diabetes are different in obese than in non-obese subjects, we conducted another GWAS to investigate the genes more significantly associated with prevalent diabetes stratified in non-obese and in obese subjects in the sample of participants from different centers.

By stratifying according to obesity it is observed that there is very little genetic overlap in the most significant genes associated with diabetes. **In non-obese individuals the top-ranked diabetes-associated SNP** in this population was the rs4911429 SNP in the MAP1LC3A (microtubule associated protein 1 light chain 3 alpha) gene, also known as LC3. Microtubule-associated proteins (MAPs), regulates microtubule stability and plays a critical role in neuronal development and plasticity. MAP1LC3A belongs to the family of MAP1 LC3 proteins that form mature complexes with MAP1A and MAP1B, which are believed to be important in the formation and development of axons and dendrites. MAP1LC3A is one of three isoforms of MAP1LC3, the mammalian homolog of yeast atg8, an essential autophagic protein. In a study by Portilla Fernandez et al., (2019), in which they studied the relationship between autophagy SNPs and cardiometabolic parameters, found a significant association between a SNP in the MAP1LC3A gene and cardiovascular disease in the Rotterdam study. Although this gene has been linked to diabetes in experimental studies, the association in GWAS is not known. Thus, we have obtained a novel result that should be investigated in more detail. The results with the PARVB gene (parvin beta), also top-ranked, are new. This gene encodes a member of the parvin family of actin-binding proteins, which play a role in cytoskeleton organization and cell adhesion. These proteins are associated with focal contacts and contain domains of calponin homology that bind to actin filaments. This family member binds to alphaPIX and alpha-actinin and can inhibit integrin-bound kinase activity. This protein also works in suppressing some tumours. Little is known about the association of the SNP with diabetes. In Asian

populations (Kumar et al., 2019; J Genet) the PARVB gene has been associated with increased risk of non-alcoholic fatty liver (NAFLD), which is characterized by the accumulation of fat in the liver with no history of chronic consumption of alcohol. The third most significant gene associated with diabetes in non-obese people is RAD52 (DNA repair protein RAD52 homolog), involved in repairing double-stranded DNA breaks. It plays a central role in genetic recombination and DNA repair by promoting complementary single-stranded DNA annealing and by stimulating RAD51 recombinase. The other top-ranked genes are involved in various metabolic pathways. We are currently completing a pathways and gene-enrichment analysis to better understand the potential functionality. We are also working on replication in other populations. This is very important to increase the causality of the associations. As with non-obese people, we performed a stratified analysis to identify the genes most associated with diabetes prevalent in obese individuals.

The SNP most associated with the prevalent risk of diabetes in obese people was the rs706282 in the TRIO gene (rio Rho guanine nucleotide exchange facto r). TRIO is a candidate gene for cognitive impairment. TRIO is a well-preserved Rho GTPase regulator that is highly expressed in the developing brain. However, little is known about the specific events regulated by TRIO during brain development and its clinical impact on humans when mutated (Ba W et al., 2015; Hum Mol Genet). Second is the most significant SNP rs9384832 in the CDH22 gene (Cadherin 22). This gene is a member of the cadherin superfamily. The gene product consists of five cadherin-repeating domains and a cytoplasmic tail similar to the highly conserved cytoplasmic region of cadherins. Expressed predominantly in the brain, this putative calcium-dependent cell adhesion protein may play an important role in morphogenesis and tissue formation in neuronal and non-neuronal cells during the development and maintenance of the brain and neuroendocrine organs. This gene has been associated with diabetes in many studies. In 2008, Bento et al., already indicated the association of several SNPs in this gene with diabetes and suggested the presence of heterogeneity in the associations. The other SNPs identified have diverse functionality and we are currently working on better characterization.

Subsequently we proceeded to create a **GRS with the top-ranked SNPs** taking into account some basic premises, among them that the MAF of the included SNPs was relatively high, that the SNPs were not in linkage disequilibrium, and that the number

of SNPs was not so high as to minimize the cost of the determinations. We initially created unweighted GRS and by relevance we chose 19 SNPs for both the GRS of non-obese people and the GRS of obese people. For both GRS a standardized variable of GRS has been created with zero mean and standard deviation the unit to be able to compare the results better. First, a logistic regression model was created in which prevalent diabetes was the dependent variable and each of the GRS (GRS_19_obes or GRS_19_No_ob) was used to explain diabetes globally regardless of whether the person is obese or non-obese.

-Calculating the OR for diabetes prevalent in the whole population for each standard deviation of the standardized GRS variable created for non-obese subjects, an OR of 1.63 (95% CI: 1.44-1, 83); P = $1.4x10^{-5.}$

-Calculating the OR for prevalent diabetes for each standard deviation of the standardized GRS variable created for obese subjects, an OR of 1.80 (95% CI: 1.60-2.02) is obtained; P = $4.4x10^{-23.}$

This indicates that in many studies statistically significant associations have been obtained for SNPs or GRS in the overall population, without these SNPs or GRS being significant or predictive for the different groups of individuals as we will see below:

→Calculation of the association of the GRS19 No_ob to estimate (by SD) the genetic risk of prevalent diabetes in non-obese subjects: OR: 2.34 (95% CI: 1.95-2.80); P = $1.04x10^{-19}$
→Calculation of the association of the GRS19-No_ob to estimate (by SD) the genetic risk of prevalent diabetes in obese subjects: OR: 1.09 (95% CI: 0.92-1.31); P = 0.289
→Calculation of the association of the GRS19-Obes to estimate (for SD) the genetic risk of prevalent diabetes in obese subjects: OR: 3.83 (95% CI: 3.08 to 4.76); P = $1.43\ x10^{-33}$
→Calculation of the association of the GRS19-Obes to estimate (for SD) the genetic risk of prevalent diabetes not obese: OR 1.01 (95% CI: 0.86 to 1.17); P = 0.989.
These results clearly show the specificity of the associations since a GRS created for obese people has a great association with the risk of prevalent diabetes in obese subjects. However, the same GRS does not present any association for non-obese subjects and vice versa. These results show the great diversity in predictive capacity of

GRS and the outlines the need to conduct more personalized investigations instead of applying the generalized ones.

Likewise, we calculated the ROC curves of the genetic GRS for prevalent diabetes in non-obese subjects and in obese people. The GRS achieved a good predictive value for the GRS19-No_obs in the non-obese (AUC: 0.71; $p = 2.5 \times 10^{-21}$), but the predictive of the GRS19_Obes was not statistically associated in non-obese subjects. Likewise, the obese GRS19 has a high AUC in the obese subjects (AUC: 0.81; $p = 9.5 \times 10^{-47}$), but in these obese subjects, the non-obese GRS19 was not statistically significant in predicting diabetes.

Currently in precision medicine it is very important to take into account the **homogeneity or heterogeneity by sex**. Our group published a Guide to analyze these differences in studies of nutritional genomics (Corella et al., 2019) and we have applied the recommendations to this project. Therefore, in all analyses we studied the possible homogeneity or heterogeneity by sex in the stratified analyses in men and women and also tested the statistical significance of the interaction term between genetic variants or GRS and sex. In this case, the effect of obesity-specific GRS19 on the risk of prevalent diabetes presents a great homogeneity in men and women and in both groups we can observe the specific effect of GRS.

In studying the effect of interaction with Mediterranean diet on the effect of specific obese and non-obese GRS we did not obtain statistically significant interactions. We will have to study this in more depth and analyze specific components of the Mediterranean diet. When studying the genes of diabetes according to adherence to the Mediterranean diet we obtained interesting results. For the high adherence to the Mediterranean diet we found as top-ranked a SNP in the CUL5 gene. This well-known CUL5, previously associated with diabetes, has a binding protein ligase ubiquitin activity. It is involved in the regulation of cytosolic calcium ion concentration and in the response to osmotic stress. It is located in the cytoplasm, core, and plasma membrane. Human CUL5 ortholog participates in the proteasome degradation pathway involving high dependent ubiquitin ligases; and the ubiquitin / proteasome degradation pathway. The gene SMAD7 (Mothers Against Decapentaplegic Homolog 7) is also detected in this group. The protein encoded by this gene is a nuclear protein that binds the ubiquitin E3 SMURF2 ligase. Upon binding, this complex is transferred to the

cytoplasm, where it interacts with the TGF-beta type-1 receptor (TGFBR1), resulting in degradation of the encoded protein and TGFBR1. Expression of this gene is induced by TGFBR1.

In the study of diabetes incidence in non-diabetic subjects, the SNP top-ranked in the GWAS was an intergenic SNP on chromosome 22. With the most relevant top-ranked SNPs we created a GRS including 28 SNPs for incident diabetes (GRS_BTBD8_rs563113 GRS_C1orf146_rs + 35513239 + GRS_CAB39L_rs12429253 GRS_CHL1_rs13093895 GRS_COL24A1_rs593146 GRS_CSGALNACT1_rs3802328 GRS_CYP2C18_rs1326832 GRS_CYP2C19_rs4641393 GRS_CYP2C9_rs12569850 + GRS_DMBX1_rs6683116 GRS_DOCK9_rs11842122 GRS_EMC8_rs2291658 + GRS_FAM107B_rs4750540 GRS_GABRB3_rs17738349 GRS_GLMN_rs7524120 + GRS_HELLS_rs2025445 GRS_intg_rs6662618 GRS_ISPD_rs1918259 + GRS_LOC105369617_rs867167 GRS_NOC3L_rs17109928 GRS_NOS2_rs944722 + GRS_NPY6R_rs12652106 GRS_PDZD2_rs6874198 + GRS_PRKCE_rs11898209 GRS_PSG9_rs8109311 GRS_RBMS3_rs9819610 + GRS_SPATA13_rs7987854 GRS_TSHZ2_rs200602). This GRS was strongly associated with diabetes incidence in non-diabetic subjects. The AUC was (AUC: 0.79; 95% CI: 0.75-0.84), showing a highly significant association (P = 1.2x $10^{-25)}$. When stratified into obese and non-obese, the GRS has slightly more predictive in non-obese (AUC: 0.83; P = 7x$10^{-15)}$ than in obese subjects (AUC: 0.77; P = 8 x$10^{-13)}$. In men and women the associations were similar, although slightly higher in women (AUC: 0.86; P = 1x10^{-9} in non-obese women). We subsequently estimated the risk (HR) of incident diabetes using a Cox regression model. The GRS variable was used as continuous. We standardized this continuous variable to better compare the estimates of the different models. The HR obtained for incident diabetes per standard deviation was: HR: 1.78 (95% CI; 1.52-2.08); P = 5.4x$10^{-13.}$ This is a very significant and relevant association in magnitude. The magnitude of the association was slightly higher in non-obese (HR: 2.07) than in obese (HR1.71) subjects.

In the pilot study at the **epigenome-wide level** we found differentially methylated genes in diabetics and non-diabetics. For example the KIRREL3 gene (kin of irregular chiasm-like protein 3), has been detected as a top-ranked CpG island differentially methylated between both groups. Interestingly, we detected top-ranked SNPs in the KIRREL3 gene also in analyzing genetic polymorphisms associated with prevalent

diabetes. The protein encoded by this gene is a member of the nephrine-like protein family and belongs to the immunoglobulin superfamily. It is expressed in fetal and adult brain, and also in renal glomerular podocytes. Mutations in this gene are associated with several neurological and cognitive disorders (Bhalla et al., 2008; Am J Clin Gent). Subsequently, associations of polymorphisms in the KIRREL3 gene with diabetes have also been described (Muller et al., 2013; Human Genetics). Most genes on the list of differential methylation between diabetics and non-diabetics have been previously described as experimentally or genetically associated with diabetes. For example, we would like to highlight the TXNIP gene (Thioredoxin-interacting protein). It has been found that the TXNIP gene was more induced by glucose in a microarray of human pancreatic islets, increased in diabetes and that its over expression leads to apoptosis of beta cells. Reducing the expression of TXNIP has shown favorable effects since it occurs a decrease in apoptosis of beta cells, increased the mass healthy beta cells, increased insulin levels and protection against diabetes (Thielen et al., 2018; Diabetes). Therefore, the integrated analysis of the different top-ranked genes in methylation is of great interest in obtaining more information about the functionality of the genes and validating associations by increasing consistency. In **the epigenome-wide methylation study** we also analyzed **the differences in methylation between obese diabetic subjects and non-obese diabetic subjects**. The methylation site with the most statistically significant differences ($P = 4.3 \times 10^{-8)}$ between obese and non-obese diabetics was cg15563355 in the SERF2 gene (Small EDRK-rich factor 2). Finally, we studied whether there are differences in methylation in diabetics who have a high adherence to the Mediterranean diet compared to diabetics who have a low adherence to it. We analyzed individual genes as well as pathways. The signaling pathway of the apelin was highly significant. These results are very new and interesting. Apelin is a peptide known as the G protein-coupled receptor ligand APJ. There are several active forms of apelin. Apelin has been shown to be involved in the regulation of cardiovascular and fluid homeostasis, food intake, cell proliferation, and angiogenesis. In addition to being a ubiquitous peptide, apelin is also produced and secreted by adipocytes and is therefore considered an adipokine.

Selection of polymorphisms, creation of GRS and association analyses in the whole sample of participants in the PREDIMED study: Influence on incident diabetes, influence on cardiovascular disease and modulation by diet. We selected 42 SNPs for the genotyping in the whole sample of PREDIMED participants. We analyzed

associations with diabetes prevalence at baseline as well as diabetes incidence in non-diabetic subjects. We created a GRS using SNPs with the most significant associations with diabetes prevalence in the whole population,. This GRS has a **strong association with diabetes prevalence** in the total population studied. In a model adjusted for sex, age, center and obesity, the GRS (standardized) was significantly associated (by standard deviation) with prevalent diabetes with OR: 1.31; P = $3.1x10^{-22.}$
Interestingly, we observed that in the total non-diabetic population, the GRS created for prevalent diabetes was significantly associated with diabetes incidence: HR: 1.21 (95% CI: 1.07-1.37); P = 0.003.

We observed a statistically significant interaction between this GRS and adherence to Mediterranean diet, so that in people with greater adherence to the Mediterranean diet, the GRS was not associated with incident diabetes (HR 1.09, P = 0.549), suggesting that a healthy Mediterranean diet neutralizes genetic susceptibility. In the group of low adherence to the Mediterranean diet, the GRS was significantly associated with an increased risk of diabetes incidence (HR: 1.54; P = 0.001). Subsequently, we analyzed the influence of the different components of the Mediterranean diet on the modulation of genetic risk by determining the incidence of diabetes. With several of the components we obtained significant results, but the most relevant of them all in the modulation counteracting the genetic risk was the intake of **vegetables**.

Therefore, we created a vegetable consumption variable based on the population mean. We considered the category of low vegetable consumption (below the mean) and high vegetable consumption (above the mean). To better illustrate the dose-response relationship of how vegetable consumption modulates the genetic risk of diabetes in its incidence, we used a genetic risk variable with three categories. We used tertiles of the continuous GRS. A statistically significant interaction was obtained (P <0.05). When vegetable consumption was low, the GRS was highly associated with diabetes incidence. This was increasingly observed, according tertiles (HR 2.10; P = 0.0004 from high tertile GRS to the lower tertile). However, in subjects with high vegetable consumption, the GRS was not significantly associated with diabetes incidence, especially in people at higher genetic risk located in the upper tertile (HR = 1.09; P = of 0.725 higher tertiles vs low tertile). Moreover, *a GRS specific for incident diabetes was computed.* The HR for this GRS was 1.54 (95% CI: 1.35-1.75); P = $1.44x10^{-10}$ by standard deviation. This association is much higher and statistically

significant than the one we had found for GRS created for prevalent diabetes, which in turn was also significantly associated with diabetes incidence. This result confirmed the specificity of genetic polymorphisms studied when analyzed association was prevalence or diabetes incidence.

We also studied the association between the GRS of incident diabetes and the occurrence of **cardiovascular diseases** during the same follow-up period. The cardiovascular event variable included the three major cardiovascular events (heart attack, stroke, and cardiovascular mortality). In considering the population as a whole, the GRS for incident diabetes was associated with increased risk of cardiovascular disease. The estimated effect for the dichotomous variable was HR: 1.34 (95% CI: 1.03–1.74); P = 0.028 in the multivariate model. These results, in which the genetic variants that confer the highest risk of incidental diabetes are also associated with increased cardiovascular risk, may reflect the "common soil", which has been published many times according to which diabetes and cardiovascular disease would share many genetic risk factors. We also found a modulation **by the Mediterranean diet** in the effect of the GRS for diabetes incidence on the occurrence of cardiovascular diseases. When adherence to the Mediterranean diet was low (less than 9 points on the scale), the diabetes GRS was associated more significantly with the risk of cardiovascular disease: HR: 1.55; 95% Cl: 1.07-2.23); P = 0.018. However, when adherence to Mediterranean diet was high, the same GRS did not show a statistically significant association with the incidence of cardiovascular diseases: *HR: 1.14; 95% Cl: 0.78-1.66; P = 0.507*. These results show that although there is a greater genetic susceptibility, this can be counteracted or minimized with a healthy dietary pattern, specifically a high adherence to the Mediterranean diet. In addition to testing the effect of adherence to the Mediterranean diet (longer-term diet pattern), we also tested the effect of the intervention variable with Mediterranean diet (short-term effect) on the association between the GRS for diabetes incidence on the incidence of cardiovascular diseases. Also for this variable we observed that the risk of cardiovascular disease was higher in people in the control group (HR: 1.79; 95% CI: 1.14-2.80; P = 0.012) than in people in the intervention group with Mediterranean diet (HR: 1.19; 95% CI: 0.87-1.66; P = 0.274) despite having the same genetic susceptibility. These results are relevant, but need replication in other populations to have a higher level of evidence. We are currently extending these results to participants in the PREDIMED study for whom we are collecting other omics data. We are also comparing associations at the

genome, epigenome and metabolome levels on diabetes and cardiovascular risk factors in another similar cohort, the PREDIMED Plus participants in Valencia.

Finally, although the statistical data analysis was carried out following the methodology proposed in the initial work plan, and many of the most significant results have been presented in previous sections, currently we are doing a new optimized data analysis, incorporating new methods of "machine learning" even though they were not initially planned in the application.

3. Relevance and possible future implications

The results of the project are very relevant. We have investigated the genetic determinants of diabetes in the elderly in general and also taking into account the influence of obesity. We used both the genome-wide association study (GWAS) approach and the candidate gene approach that has been important in other populations. With this we have constructed genetic risk scores (GRS) associated with the risk of prevalent diabetes, diabetes incidence, and cardiovascular diseases. Each of the GRS created has shown specific associations, indicating the importance of taking into account the characteristics of the population (both demographic and geographical) and the phenotype studied (incidence, prevalence, obesity, etc.) when conducting genomic research with possible applications in precision medicine.

We found great heterogeneity in the GRS associations due to obesity, obtaining a combination of polymorphisms (GRS) that are associated with diabetes only in obese people, while another combination of polymorphisms (GRS) was associated with diabetes in non-obese subjects. We have calculated the predictive value of these GRS showing that if we apply an obese GRS to non-obese subjects, the predictive value is almost nil and vice versa. This is very relevant for the applications of genetic testing because until now the starting phenotypic characteristics of the tested person were not considered, and in our study we have shown that it is crucial. We also analyzed the data from a gender perspective and found differences in the predictive values of genetic polymorphisms and GRS between men and women in some analyses, providing more evidence to consider the sex variable relevant in future precision medicine. The findings indicate that the paradigm in the construction of GRS needs to be changed to

improve their usefulness. There is currently a trend to increase the number of SNPs in the GRS to improve their predictive value regardless of the characteristics of the population to which they apply. This is not giving good results and many authors have indicated that the GRS are the least accurate of precision medicine. By changing the way by which the GRS are generated, focusing on the demographic and phenotypic characteristics of the population, as well as defining more precisely the phenotype to be predicted (prevalent diabetes or incident diabetes at a given time for example), we have shown that there are increases in the predictive value and the magnitude of the associations. On the other hand, our results have also shown that the effect of genetic susceptibility to both diabetes and cardiovascular disease is not deterministic but can be counteracted by the Mediterranean diet. This is very relevant in its application for preventive measures. Although our results may not have an imminent clinical application, they do serve to reorient research in genomic medicine and personalized prevention for future precision medicine or more personalized precision nutrition.

4. Generated publications

Currently we have published 12 articles including results and methodology derived from the project. We are still writing more articles with the main results. Until the recent completion of all genomic analyzes it was not possible to publish the overall results, and partial results have been published. Many more papers with integrated project results will be submitted in the coming months. The published articles are listed below. In all of them, the La Marató de TV3 project has been mentioned, indicating its reference.

1-Corella D, Coltell O, Macian F, Ordovás JM. Advances in Understanding the Molecular Basis of the Mediterranean Diet Effect. Annu Rev Food Sci Technol. 2018;9:227-249.

2-Corella D, Coltell O, Portolés O, Sotos-Prieto M, Fernández-Carrión R, Ramirez-Sabio JB, Zanón-Moreno V, Mattei J, Sorlí JV, Ordovas JM. A Guide to Applying the Sex-Gender Perspective to Nutritional Genomics. Nutrients. 2018 Dec 20;11(1). pii: E4.

3-Corella D, Barragán R, Ordovás JM, Coltell Ó. [Nutrigenetics, nutrigenomics and Mediterranean diet: a new vision for gastronomy]. Nutr Hosp. 2018;35(Spec No4):19-27.

4-Corella D, Ordovás JM. [The role of omics in precision nutrition: strengths and weaknesses]. Nutr Hosp. 2018 12;35(Spec No4):10-18.

5-Papandreou C, Li J, Liang L, Bulló M, Zheng Y, Ruiz-Canela M, Yu E, Guasch-Ferré M, Razquin C, Clish C, Corella D, Estruch R, Ros E, Fitó M, Arós F, Serra-Majem L, Rosique N, Martínez-González MA, Hu FB, Salas-Salvadó J. Metabolites related to purine catabolism and risk of type 2 diabetes incidence; modifying effects of the TCF7L2-rs7903146 polymorphism. Sci Rep. 2019;9(1):2892.

6-Coltell O, Asensio EM, Sorlí JV, Barragán R, Fernández-Carrión R, Portolés O, Ortega-Azorín C, Martínez-LaCruz R, González JI, Zanón-Moreno V, Gimenez-Alba I, Fitó M, Ros E, Ordovas JM, Corella D. Genome-Wide Association Study (GWAS) on Bilirubin Concentrations in Subjects with Metabolic Syndrome: Sex-Specific GWAS Analysis and Gene-Diet Interactions in a Mediterranean Population. Nutrients. 2019 Jan 4;11(1):90.

7-BIRTH-GENE (BIG) Study Working Group, Huang T, Wang T, Zheng Y, Ellervik C, Li X, Gao M, Fang Z, Chai JF, Ahluwalia TVS, Wang Y, Voortman T, Noordam R, Frazier-Wood A, Scholz M, Sonestedt E, Akiyama M, Dorajoo R, Zhou A, Kilpeläinen TO, Kleber ME, Crozier SR, Godfrey KM, Lemaitre R, Felix JF, Shi Y, Gupta P, Khor CC, Lehtimäki T, Wang CA, Tiesler CMT, Thiering E, Standl M, Rzehak P, Marouli E, He M, Lecoeur C, Corella D, Lai CQ, Moreno LA, Pitkänen N, Boreham CA, Zhang T, Saw SM, Ridker PM, Graff M, van Rooij FJA, Uitterlinden AG, Hofman A, van Heemst D, Rosendaal FR, de Mutsert R, Burkhardt R, Schulz CA, Ericson U, Kamatani Y, Yuan JM, Power C, Hansen T, Sørensen TIA, Tjønneland A, Overvad K, Delgado G, Cooper C, Djousse L, Rivadeneira F, Jameson K, Zhao W, Liu J, Lee NR, Raitakari O, Kähönen M, Viikari J, Grote V, Langhendries JP, Koletzko B, Escribano J, Verduci E, Dedoussis G, Yu C, Tham YC, Lim B, Lim SH, Froguel P, Balkau B, Fink NR, Vinding RK, Sevelsted A, Bisgaard H, Coltell O, Dallongeville J, Gottrand F, Pahkala K, Niinikoski H, Hyppönen E, Pedersen O, März W, Inskip H, Jaddoe VWV, Dennison E, Wong TY, Sabanayagam C, Tai ES, Mohlke KL, Mackey DA, Gruszfeld D, Deloukas P, Tucker KL, Fumeron F, Bønnelykke K, Rossing P, Estruch R, Ordovas JM, Arnett DK, Meirhaeghe A, Amouyel P, Cheng CY, Sim X, Teo

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Conference papers:

We have presented several papers at conferences in the form of a poster or oral communication, as well as several invited talks. Among them we would like to mention the following:

- Several invited talks for Dr Corella on the occasion of having received the Jaume I Prize for Medical Research 2018, in which she disseminated some preliminary results of this project in different forums.
- The invited talk of Dr Corella at the Las Vegas Obesity Congress held in 2019 in which she presented GWAS results in Mediterranean population modulating obesity and diabetes.
- Dr Corella was an invited speaker at the Congress of the Spanish Diabetes Society (June 2020) to present on gene-diet and GRS interactions in determining diabetes risk.