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ABSTRACT

Metabolic syndrome (MetS) has become a health and financial burden worldwide. The MetS definition captures clustering of risk factors that predict higher risk for diabetes mellitus and cardiovascular disease. Our study hypothesis is that additional to genes influencing individual MetS risk factors, genetic variants exist that influence MetS and inflammatory markers forming a predisposing MetS genetic network. To test this hypothesis a staged approach was undertaken. (a) We analyzed 17 metabolic and inflammatory traits in more than 85,500 participants from 14 large epidemiological studies within the Cross Consortia Pleiotropy Group. Individuals classified with MetS (NCEP definition), versus those without, showed on average significantly different levels for most inflammatory markers studied. (b) Paired average correlations between 8 metabolic traits and 9 inflammatory markers from the same studies as above, estimated with two methods, and factor analyses on large simulated data, helped in identifying 8 combinations of traits for follow-up in meta-analyses, out of 130,305 possible combinations between metabolic traits and inflammatory markers studied. (c) We performed correlated meta-analyses for 8 metabolic traits and 6 inflammatory markers by using existing GWAS published genetic summary results, with about 2.5 million SNPs from twelve predominantly largest GWAS consortia. These analyses yielded 130 unique SNPs/genes with pleiotropic associations (a SNP/gene associating at least one metabolic trait and one inflammatory marker). Of them twenty-five variants (seven loci newly reported) are proposed as MetS candidates. They map to genes *MACF1*, *KIAA0754*, *GCKR*, *GRB14*, *COBLL1*, *LOC646736-IRS1*, *SLC39A8*, *NELFE*, *SKIV2L*, *STK19*, *TFAP2B*, *BAZ1B*, *BCL7B*, *TBL2*, *MLXIPL*, *LPL*, *TRIB1*, *ATXN2*, *HECTD4*, *PTPN11*, *ZNF664*, *PDXDC1*, *FTO*, *MC4R* and *TOMM40*. Based on large data evidence, we conclude that inflammation is a feature of MetS and several gene variants show pleiotropic genetic associations across phenotypes and might explain a part of MetS correlated genetic architecture. These findings warrant further functional investigation.

1. Introduction

Metabolic syndrome (MetS) is a constellation of medical conditions that include abdominal obesity with visceral fat deposition, atherogenic dyslipidemia (high triglyceride and low high density lipoprotein cholesterol levels), hyperglycemia and/or insulin resistance, and high blood pressure [1]. Due to the rise in obesity rates and poor dietary habits, MetS has become an increasing public health and financial burden [2–7]. MetS is associated with at least five-fold increased risk in developing diabetes mellitus (T2D) and two-fold increased heart disease risk [5]. Recently, it was reported that individuals with acute ischemic stroke and metabolic syndrome have increased

inflammation and arterial stiffness [8,9]. Overall MetS captures a confluence of clinical disorders, assisting front-line practitioners in identifying cardiovascular and metabolic risk factors requiring simultaneous clinical attention [1,10].

There are differing ideas regarding the genetic etiology and cardiovascular sequelae of MetS, including whether the MetS components are independent in origin or share common determinants. At the phenotypic level, the increased cardiovascular disease (CVD) risk associated with MetS appears to be no greater than the sum of its single traits' risk [11,12].

Individuals with MetS, often exhibit a pro-inflammatory state, with increased levels of C-reactive protein, white blood cell count, coagulation factors VII, VIII and fibrinogen, von Willebrand factor, plasminogen activator inhibitor 1, soluble vascular adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), P-selectin as well as decreased levels of adiponectin [13–17]. It has been suggested that modified cytokine expression associating a greater volume of adipose tissue may be a mechanism for the low grade inflammation accompanying dysregulated lipid and glucose metabolism, as well as blood pressure [13,18,19]. Henneman et al. [12] recommended the genetic dissection of MetS be approached by studying individual components, because of their high heritability. Currently, it remains unclear whether genetic variants identified for individual metabolic traits [20–24] and inflammatory markers [25–29], have pleiotropic effects, thereby influencing the correlated architecture of these traits. Dallmeier et al. [30] suggested that the relationship between MetS and a number of inflammatory markers is largely accounted for by the individual MetS components, and MetS as a construct generally is no more than the sum of its parts with respect to inflammation. We propose that in addition to genes influencing individual MetS risk factors, there are genetic variants that influence MetS risk factors and inflammatory markers, forming a pleiotropic intertwined genetic network. As part of the "Pleiotropy among Metabolic traits and Inflammatory-prothrombotic markers" working group, a sub-group of the *Cross Consortia Pleiotropy Group*, we aimed to: (a) evaluate epidemiological associations between MetS and inflammatory markers; (b) assess correlations among metabolic traits and inflammatory markers for identifying combinations to explore for potentially genetic pleiotropic associations and pathways; (c) utilize these newly identified trait-combinations to perform correlated meta-analyses using previously published GWAS meta-results from large consortia for the individual traits, with the overall goal of detecting MetS candidates with potential pleiotropic effects across metabolic traits and inflammatory markers.

2. Materials and methods

2.1. A brief summary of implemented methods

The international collaboration of Cross Consortia Pleiotropy Group (XC-Pleiotropy) was founded in the early 2011 for studying pleiotropy by using published GWAS results. The PMI-WG is a collaborative group within the XC-Pleiotropy (Supplement 1). For implementing the first two aims (see Introduction), 17 metabolic traits and inflammatory markers are studied (Section 2.1.1), from 14 large-scale cohort studies (dependent on cohort-specific assay availability, Table 1.a and Supplement 2). Together these data represent more than 85,500 individuals (Supplemental Table 1). Laboratory methods for obtaining these traits are described in Supplement 2. Trait adjustments for medication use and other covariates are provided in Section 2.1.2. Methods of estimating correlations with simulations and Fisher's Z-transformation are provided in Section 2.1.3, and factor analysis in Section 2.1.4. Each study was approved by its local ethics board and each participant provided written, informed consent.

For implementing the third aim (see Introduction), we utilized published full results from mainly GWAS meta-analyses consortia (Table 1.b). We performed meta-analyses taking correlation among results into consideration [31,32] (Section 2.1.5) for identifying pleiotropic variants for metabolic traits and inflammatory markers. In this paper, a leading SNP and its mapped gene are considered pleiotropic when the SNP associates with at least a metabolic trait and an inflammatory marker and passes the meta-analysis threshold. In this framework, our study includes published results for body mass index (BMI) [23], waist circumference (WAIST) [33], high density lipoprotein cholesterol (HDLC) and triglycerides (TG) [24], fasting glucose (GLUC) and fasting insulin (INS) [20], systolic and diastolic blood pressure (SBP, DBP) [22]. In addition, our meta-analyses included inflammatory markers, C-reactive protein (CRP) [25], plasminogen activator inhibitor 1 (PAI-1) [26], white blood cell counts (WBCC) [27], adiponectin (ADIP) [34], intercellular adhesion molecule 1 (ICAM-1) [28], and interleukin 6 (IL-6) [35]. Because interleukin 10 (IL-10) was not significantly correlated with other traits, and fibrinogen (FIB) and tumor necrosis factor alpha (TNFA) meta-analyses GWAS results were not available, (although analyzed when studying correlations), these three traits are not present in our final meta-analyses. The reported allele frequencies were based on GIANT BMI. When the SNP was not studied in GIANT consortium BMI, then allele frequencies from MAGIC consortium GLUC were used. We also used bioinformatics approaches for appraising pleiotropy (Section 2.1.6).

2.1.1. Traits studied

To evaluate the associations between inflammatory markers and MetS risk factors, seventeen traits were studied. Metabolic traits included were BMI (kg/m^2) and WAIST (in cm) representing domains of adiposity/obesity, for lipids HDLC (mg/dL) and fasting (at least 8 h) TG (mg/dL), for glucose metabolism and insulin, fasting INS (mU/L) and fasting GLUC (mg/dL), for blood pressure SBP and DBP (mm Hg, as average of all three, or the 2nd and 3rd seating blood pressure measures). We use the term "inflammatory markers" for brevity when referring to the inflammatory–prothrombotic markers. Inflammatory markers studied were fibrinogen (FIB) (mg/dL) and PAI-1 (IU/mL) representing prothrombotic markers, and CRP (mg/L), tumor necrosis factor alpha (TNF-alpha) (pg/mL), ICAM-1 (ng/mL), IL-6 (pg/mL),

Table 1.a
XC-Pleiotropy studies for assessing associations among MetS and inflammatory markers and identifying promising trait combinations for evaluating the role of pleiotropy in MetS etiology.

No Participating studies	Acronym	Cohorts	~N
1 The Atherosclerosis Risk in Communities Study	ARIC	AA and EA	4,251; 11,462
2 The Coronary Artery Risk Development in Young Adults	CARDIA	EA	2,448
3 The Johns Hopkins Genetic Study of Atherosclerosis Risk	GeneSTAR	AA and EA	1,335; 2,106
4 The Genetic Epidemiology Network of Arteriopathy	GENOA	AA and EA	1,477; 1,238
5 The Family Heart Study	FamHS	EA	5,537
6 The Framingham Heart Study	FHS	EA	7,407
7 The INTER99	INTER99	EA	6,783
8 The LifeLines Cohort Study		EA	13,295
9 The Rotterdam Study	RS	EA	4,170
10 The Women's Genome Health Study	WGHS	EA	23,186
11 The Women's Health Initiative	WHI	EA	934

Note: The addition of a suffix AA in the study name refers to an African American ancestry cohort, and EA refers to a European ancestry cohort.

Table 1.b
Sources of meta-analyses and GWAS tests results analyzed in our 9 correlated meta-analyses.

No	Contributing studies	Acronym	Traits	Studies (N)	Participants (N)	SNPs (N)	Reference
1	The Genetic Investigation of Anthropometric Traits Consortium	GIANT	BMI, WAIST	28	~124,000	~2.5 M	[23,33]
2	The Global Lipids Genetics Consortium	GLGC	HDLC, TG	46	~99,000	~2.5 M	[24]
3	The Meta-Analyses of Glucose and Insulin-related traits	MAGIC	GLUC, INS	21	~46,000, 38,000	~2.5 M	[20]
4	The Global BPgen	GBPG	SBP, DBP	17	~34,000	~2.5 M	[22]
5	The Cohorts of the Heart and Aging Research in Genomic Epidemiology Consortium	CHARGE					
6	and The European Special Population Network	EUROSPAN	CRP	15	~66,185	~2.5 M	
7	and six independent studies						[25]
8	Independent cohorts of European-ancestry		PAI-1	8	~19,599	~2.5 M	[26]
9	The Cohorts of the Heart and Aging Research in Genomic Epidemiology Consortium	CHARGE	WBCC	7	~19,509	~2.5 M	[27]
10	ADIPOGen Consortium	ADIPOGen	ADIP	23	~35,355	~2.5 M	[34]
11	The Women's Genome Health Study	WGHS	ICAM-1	1	2,435	~0.3 M	[28]
12	The Howard University Family Study	HUFS	IL-6	1	707	~5.0 M	[35]

interleukin 10 (IL-10) (pg/mL), WBCC (10e9/L) and ADIP (μg/mL) representing markers of immune or inflammatory response. The studies had a variable number of traits, dependent on the assays performed (Supplement 2). In the study of correlations, because we could not pool individual data from cohorts, we sought to find the average correlation among all traits for 14 cohorts through two methods, using simulations and using Fisher's Z-transformation. The MetS definition, data analyses methods, adjustments for medications use (for blood pressure and lipids medications) and covariates were similar for all contributing cohorts and described in Section 2.1.2.

2.1.2. MetS definition, variables' adjustments for medications and other covariates

A participant was classified with MetS when thresholds were passed for three or more out of five traits of the National Cholesterol Education Program (NCEP) improved threshold [36]: *WAIST ≥ 102 cm for men/WAIST ≥ 88 cm for women*; *GLUC ≥ 100 mg/dL*; *TG ≥ 150 mg/dL*; *HDLC < 40 mg/dL for men/HDLC < 50 mg/dL for women*; *SBP ≥ 130 mm Hg/DBP ≥ 85 mm Hg*. The MetS was based on the improved NCEP definition [36] using original traits adjusted for medication use only (in all cohorts, except for WGHS, which did not measure GLUC), representing (B) set of data (see Supplemental Tables 9–22). T2D was defined as following: *(GLUC ≥ 126 mg/dL, or using antidiabetic medications or insulin) and diabetes onset age ≥ 40 years.*

The average blood pressure was adjusted for individuals using antihypertensive medication(s) as follows, *SBP = measured SBP + 15 mm Hg*; and *DBP = measured DBP + 10 mm Hg* [37]. For individuals using anti-hyperlipidemic medications, their lipid levels were adjusted respectively as follows, *HDLC = measured HDLC / (1 + 0.04419)*; and *TG = measured TG / (1 − 0.17159)*. For lipids, adjusting constants are produced as a summary of Wu et al.'s work [38] and also from our additional unpublished summary follow-up, which combined for a total of 92 clinical trials (for HMG-CoA reductase inhibitors, Fibric Acid Derivatives, Cholesterol Absorption inhibitor, Nicotinic acid derivatives, Bile sequestrants and Fish oil) including 53,005 participants for HDLC and 53,432 participants for TG. All participating studies set to missing GLUC and INS values for individuals that were taking insulin or diabetic medications. Before performing any analysis, the participating studies made sure that each variable had a normal distribution, or transformed them to near normal. For example, a natural log transformation worked well for TG in general for all cohorts. In the FamHS, GLUC had a high kurtosis, thus applying a Box–Cox power transformation it was found, that $1/GLUC^2$ transformation worked well in acquiring a near-normal distributed GLUC. As a result, for any bivariate correlations in the FamHS that included GLUC, correlation coefficients were multiplied by (−1), because power transformation for GLUC reversed the sign compared to original corresponding correlations. As an empirical check, when compared to FHS, the GLUC correlations in FamHS were very similar, although a transformation of GLUC was implemented in the FamHS. In addition, phenotypes were adjusted for polynomial age trend (age and age^2), sex and important study specific covariates (e.g. field center), which were included in the regression model if $p < 0.05$ for generating the final data for analysis: standardized residuals, i.e. with mean 0 and variance of 1.

In the Supplemental Tables 9–22, we present statistics for individual studies for (A) original variables, (B) original variables adjusted only for medication use, and (C) residuals from regression with mean 0 and variance 1 of variables obtained from adjusting (B) data for additional covariates as mentioned above. In the correlation statistical analyses we use the standardized final residuals labeled as the (C) set of data.

2.1.3. Correlation statistical analysis and simulations

We grouped participants' data in strata with- and without MetS (M_1 versus M_0), for analyzing mean differences of inflammatory markers in these two subgroups for each cohort. We used (B) data and pooled *t*-test for testing mean differences between the two: $(\bar{x}_1 - \bar{x}_2)$, with sample sizes n_1 and n_2 via $t = \frac{(\bar{x}_1 - \bar{x}_2)}{s_{p*}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}$, where $s_p = \sqrt{\frac{(n_1-1)*s_1^2+(n_2-1)*s_2^2}{n_1+n_2-2}}$ is the pooled standard deviation and $n_1 + n_2 - 2$ degrees of freedom. In general, the MetS subgroup sample size was smaller than non-MetS one, but the variances between M_1 and M_0 subgroups were similar. The mean differences of the two groups' p-values were tested against a conservative Bonferroni p-threshold for $\alpha = 0.05$ experiment-wise, which corresponded to $p = 9.43e-04$ for 53 tests. Statistics of MetS, its risk factors as well as of inflammatory markers by cohort are summarized in Fig. 1 and Supplemental Figs. 1(a–g). The inflammatory markers' boxplot graph comparisons were built by using simulations via "rnorm" function in R with mean, standard deviation and sample size corresponding to subgroups with- and without MetS from the original data, (because in this collaboration we did not have direct access and could not pool original data at the participants' level). The above analysis was followed by correlation analyses (including up to 17 traits), performed with (C) data (defined at the end of Section 2.1.2) near normally distributed, adjusted for medication use and covariates. All pairwise correlations were performed using Pearson correlation procedure (using SAS v. 9.3 or R v. 2.15.1, presented in Supplemental Tables 9–22).

We then used two parallel approaches, simulation and Fisher's Z-transformation, to generalize pairwise average correlations over all studies and to confirm our results. First, simulation processes were implemented to produce the average correlation matrix and the final correlated simulated data across all studies (N > 85,500 individuals) based on the (C) set of data. Simulation 1 was performed following these steps: using N (largest number of participants per study) and variance–covariance matrices (from above single studies) we simulated multivariate normal distributions with mean 0 and variance of 1, of dimension (p-variables, N-participants) for each study, using an R multivariate normal generating ("mvrnorm") function of the MASS library [39]. Since in simulations we used the largest number of participants per study, next, we introduced (in random patterns) missing values in traits when they were not available in all participants of a specific

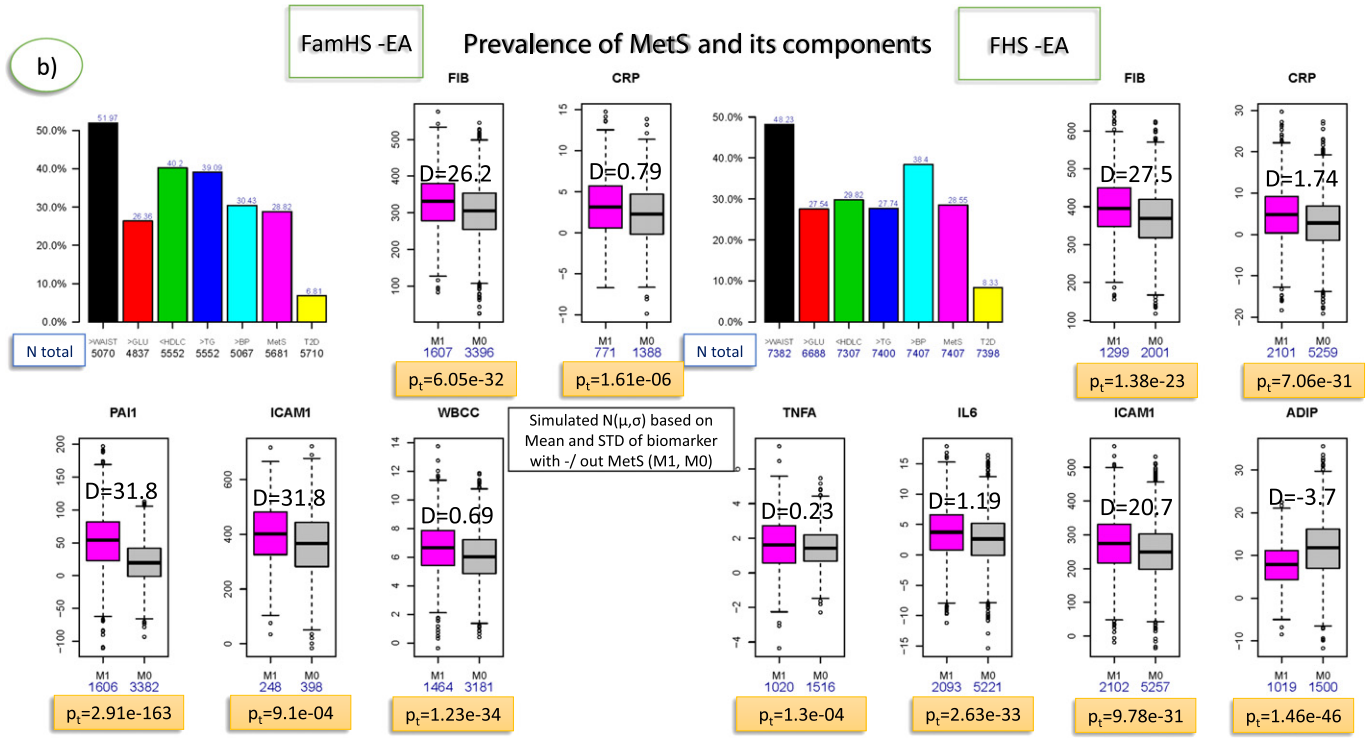

Fig. 1. Prevalence of MetS and its components and mean levels of inflammatory markers in individuals classified with and without MetS (M_1 vs. M_0). Note: Top histogram numbers represent prevalence (%) of MetS, T2D and MetS components. Bottom numbers represent number of participants for a particular trait. The inflammatory marker boxplot graph comparisons were built by using "rnorm" function in R with mean, standard deviation and sample size corresponding to subgroups with and without MetS from original (B) data. Overall, they represent 53 tests of inflammatory markers per MetS strata, summarized in Supplemental Figs. 1(a–g). The number within each pair of boxplots marked by "D=" is the difference of two means of an inflammatory marker in groups of participants classified with versus without MetS. The light yellow boxed number at the bottom of the same graph marked with "p_t=" represents a p-value calculated by pooled *t*-test for testing if their means (M_1 vs. M_0) are different. In case the color of p_t-value box is gray, then the p-value does not pass the Bonferroni threshold p = 9.43e−04.

cohort. Thus, 100 replications of simulated data imitated correlations and sample size of the original cohorts. When pooled they formed all studies' set. These data represented all traits, but with corresponding per trait missing values. Correlations of simulated data were evaluated via Pearson pairwise correlation, which produced a full variance–covariance matrix, representing a simulated approximation of the average correlation matrix of single studies. The covariance matrix (correlations among metabolic traits, metabolic traits and inflammatory markers, and among inflammatory markers) of simulation 1 are presented in Table 2. Next, simulation 2 (again 100 replications) was implemented by using the first simulation's average variance–covariance matrix, to produce multivariate standardized normal variables with p = 16 variables and N > 85,500 individuals and no missing values. Simulation 2 with 100 replications was used to conduct factor analyses.

Second, we performed Fisher's Z-transformation to average correlations of standardized final residuals of the (C) set of data (Supplemental Table 2). Assuming that correlations of any two independent bivariate samples (r_1 and r_2) of n_1 and n_2 sample sizes for the same trait combinations are random samples from a larger population, a combined correlation estimate ($\overline{r}$) can be computed. Application of the Z transformation of the two sample correlations follows: $Z_1 = \tanh^{-1}(r_1)$ and $Z_2 = \tanh^{-1}(r_2)$, where tanh is hyperbolic tangent and the Z can be calculated as $Z = 0.5 \ln(\frac{1+r}{1-r}) = \operatorname{artanh}(r)$, where artanh is hyperbolic arctangent applied to each correlation coefficient. The weighted average $\overline{Z}$ of the corresponding Z values is

$$\overline{Z} = \frac{(n_1-3)Z_1 + (n_2-3)Z_2}{n_1+n_2-6},$$

where the weights are inversely proportional to their variances ($V(\overline{Z}) = 1/(n_1+n_2-6)$). Thus, a combined correlation estimate is $\overline{r} = \tanh(\overline{Z})$. We extended averaging correlation coefficients for each bivariate trait combination to include up to 14 cohorts' correlation estimations, by writing a SAS macro program that implements Fisher's Z-transformation averaging via SAS MIANALYSE procedure. The IL-10 was dropped from these analyses, because it was present in only one study.

2.1.4. Factor analysis

Factor analyses with "Varimax" rotation were performed in SAS, v. 9.3. The purpose of using a multivariate statistical analysis was to identify latent clusters of traits that may help in identifying MetS and inflammatory markers underlying etiology. "Varimax" rotation creates orthogonal clusters of correlated variables. The objective is to maximize the independence of the clusters of correlated variables that contribute to specific factors. An absolute value of a loading 0.4 or larger (which represents a correlation of an original variable to a factor when the data are standardized) is considered in the scale of correlations as a significant contribution. To account for the stochastic process in the 100 simulations, 100 factor analyses (p = 16, N > 85,500) with "Varimax" rotation were considered (Supplemental Fig. 2). A coefficient of congruence was calculated as: $\left(CC = \frac{\sum_{n=1}^{ntraits} l_1 l_2}{\sqrt{\left(\sum_{n=1}^{ntraits} l_1^2\right)\left(\sum_{n=1}^{ntraits} l_2^2\right)}}\right)$, where l_1 represents loadings of a factor in a replication, l_2 represents loadings of a similar factor in another replication and *ntraits* is the number of traits contributing to a particular factor [40]. This similarity coefficient was calculated for all similar factors in the 100 replications (respectively $100 * 99/2 = 4{,}950$ times) as an average similarity measure of comparable factor configurations in the simulations (Supplemental Table 3).

Table 2
Average correlations and their lower and upper r estimates for 100 replications of simulated metabolic traits and inflammatory markers (emulating 100 sets of 14 cohorts' real data, p = 17, N > 85,500) simulated with missing values (simulation 1, see Section 2.1.3).

Correlations of metabolic traits

bmi	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	1	0.844	−0.336	0.306	0.510	0.282	0.293	0.263
sd	0	0.001	0.003	0.003	0.003	0.004	0.003	0.003
min	1	0.841	−0.344	0.299	0.502	0.272	0.286	0.257
max	1	0.846	−0.328	0.315	0.519	0.293	0.300	0.272
waist	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.844	1	−0.336	0.321	0.513	0.279	0.276	0.247
sd	0.001	0	0.003	0.003	0.003	0.004	0.003	0.003
min	0.841	1	−0.344	0.313	0.505	0.269	0.268	0.239
max	0.846	1	−0.328	0.327	0.523	0.288	0.284	0.254
hdlc	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	−0.336	−0.336	1	−0.481	−0.359	−0.175	−0.107	−0.091
sd	0.003	0.003	0	0.004	0.003	0.004	0.004	0.004
min	−0.344	−0.344	1	−0.490	−0.367	−0.183	−0.117	−0.101
max	−0.328	−0.328	1	−0.473	−0.350	−0.168	−0.101	−0.082
tg	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.306	0.321	−0.481	1	0.376	0.208	0.202	0.185
sd	0.003	0.003	0.004	0	0.004	0.004	0.004	0.004
min	0.299	0.313	−0.490	1	0.366	0.196	0.193	0.175
max	0.315	0.327	−0.473	1	0.386	0.218	0.210	0.193
ins	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.510	0.513	−0.359	0.376	1	0.355	0.209	0.205
sd	0.003	0.003	0.003	0.004	0	0.004	0.004	0.005
min	0.502	0.505	−0.367	0.366	1	0.342	0.199	0.194
max	0.519	0.523	−0.350	0.386	1	0.367	0.223	0.214
gluc	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.282	0.279	−0.175	0.208	0.355	1	0.185	0.138
sd	0.004	0.004	0.004	0.004	0.004	0	0.004	0.004
min	0.272	0.269	−0.183	0.196	0.342	1	0.176	0.125
max	0.293	0.288	−0.168	0.218	0.367	1	0.199	0.150
sbp	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.293	0.276	−0.107	0.202	0.209	0.185	1	0.742
sd	0.003	0.003	0.004	0.004	0.004	0.004	0	0.001
min	0.286	0.268	−0.117	0.193	0.199	0.176	1	0.737
max	0.300	0.284	−0.101	0.210	0.223	0.199	1	0.745
dbp	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.263	0.247	−0.091	0.185	0.205	0.138	0.742	1
sd	0.003	0.003	0.004	0.004	0.005	0.004	0.001	0
min	0.257	0.239	−0.101	0.175	0.194	0.125	0.737	1
max	0.272	0.254	−0.082	0.193	0.214	0.150	0.745	1

Note: correlation mean of 100 simulated replications, sd– standard deviation, min–minimum, and max– maximum of correlation in 100 replications
Highlighted in yellow correlation coefficents –(0.2 – < 0.4), in orange –(0.4–<0.6) and in red ≥ 0.6

Correlations of metabolic traits and inflammatory markers

fib	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.254	0.253	−0.200	0.105	0.147	0.079	0.105	0.073
sd	0.004	0.004	0.004	0.005	0.004	0.005	0.004	0.004
min	0.244	0.243	−0.209	0.093	0.137	0.067	0.098	0.064
max	0.263	0.264	−0.189	0.116	0.159	0.090	0.117	0.087
crp	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.406	0.380	−0.196	0.275	0.259	0.154	0.191	0.156
sd	0.003	0.003	0.004	0.010	0.005	0.004	0.003	0.004
min	0.399	0.374	−0.204	0.255	0.249	0.141	0.184	0.148
max	0.415	0.387	−0.187	0.290	0.273	0.166	0.199	0.166
pai1	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.444	0.447	−0.372	0.389	0.497	0.332	0.176	0.152
sd	0.008	0.008	0.009	0.008	0.008	0.009	0.009	0.009
min	0.421	0.430	−0.391	0.372	0.480	0.304	0.159	0.129
max	0.470	0.473	−0.345	0.405	0.520	0.349	0.204	0.173
il6	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.285	0.290	−0.175	0.140	0.192	0.126	0.129	0.090
sd	0.008	0.008	0.007	0.008	0.007	0.008	0.009	0.008
min	0.269	0.276	−0.192	0.121	0.176	0.108	0.111	0.070
max	0.308	0.312	−0.158	0.157	0.212	0.146	0.149	0.114
tnfa	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.098	0.094	−0.178	0.135	0.105	0.072	0.042	0.047
sd	0.011	0.011	0.009	0.010	0.009	0.009	0.009	0.010
min	0.074	0.069	−0.208	0.110	0.085	0.051	0.014	0.022
max	0.125	0.121	−0.154	0.159	0.130	0.097	0.068	0.065
icam1	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.163	0.176	−0.210	0.171	0.197	0.106	0.101	0.077
sd	0.005	0.004	0.005	0.007	0.007	0.007	0.005	0.005
min	0.154	0.165	−0.228	0.154	0.179	0.091	0.084	0.066
max	0.174	0.189	−0.201	0.183	0.219	0.126	0.113	0.091
il10	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.001	0.032	−0.069	−0.011	0.041	0.019	−0.001	0.011
sd	0.017	0.018	0.016	0.017	0.014	0.014	0.015	0.016
min	−0.041	−0.005	−0.110	−0.048	0.008	−0.011	−0.036	−0.023
max	0.055	0.087	−0.026	0.049	0.087	0.055	0.031	0.050
adip	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	−0.233	−0.244	0.399	−0.331	−0.319	−0.195	−0.075	−0.055
sd	0.006	0.006	0.005	0.005	0.006	0.007	0.006	0.006
min	−0.250	−0.255	0.385	−0.344	−0.332	−0.210	−0.091	−0.066
max	−0.219	−0.226	0.413	−0.317	−0.300	−0.177	−0.060	−0.039
wbbc	BMI	WAIST	HDLC	TG	INS	GLUC	SBP	DBP
mean	0.146	0.175	−0.195	0.236	0.168	0.095	0.120	0.067
sd	0.004	0.004	0.004	0.004	0.005	0.004	0.005	0.005
min	0.133	0.165	−0.207	0.227	0.156	0.086	0.104	0.056
max	0.153	0.184	−0.182	0.247	0.181	0.104	0.134	0.079

Correlations of inflammatory markers

fib	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	1	0.442	0.150	0.331	0.101	0.229	0.099	−0.126	0.291
sd	0	0.004	0.010	0.007	0.009	0.005	0.014	0.009	0.005
min	1	0.433	0.128	0.317	0.075	0.219	0.065	−0.147	0.279
max	1	0.452	0.171	0.347	0.119	0.239	0.145	−0.102	0.309
crp	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.442	1	0.268	0.416	0.135	0.266	0.200	−0.082	0.319
sd	0.004	0	0.008	0.008	0.010	0.004	0.015	0.006	0.005
min	0.433	1	0.247	0.398	0.110	0.257	0.157	−0.097	0.306
max	0.452	1	0.287	0.439	0.157	0.274	0.239	−0.064	0.333
pai1	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.150	0.268	1	0.141	0.160	0.210	0.060	−0.353	0.160
sd	0.010	0.008	0	0.029	0.017	0.010	0.017	0.014	0.008
min	0.128	0.247	1	0.070	0.123	0.188	0.022	−0.384	0.142
max	0.171	0.287	1	0.202	0.210	0.232	0.121	−0.309	0.180
il6	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.331	0.416	0.141	1	0.251	0.247	.	−0.130	0.234
sd	0.007	0.008	0.029	0	0.011	0.010	.	0.009	0.015
min	0.317	0.398	0.070	1	0.223	0.220	.	−0.155	0.207
max	0.347	0.439	0.202	1	0.274	0.271	.	−0.112	0.280
tnfa	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.101	0.135	0.160	0.251	1	0.253	0.099	−0.060	0.058
sd	0.009	0.010	0.017	0.011	0	0.009	0.015	0.010	0.016
min	0.075	0.110	0.123	0.223	1	0.225	0.054	−0.088	0.024
max	0.119	0.157	0.210	0.274	1	0.277	0.134	−0.036	0.099
icam1	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.229	0.266	0.210	0.247	0.253	1	0.179	−0.050	0.173
sd	0.005	0.004	0.010	0.010	0.009	0	0.014	0.007	0.009
min	0.219	0.257	0.188	0.220	0.225	1	0.140	−0.064	0.150
max	0.239	0.274	0.232	0.271	0.277	1	0.209	−0.035	0.195
il10	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.099	0.200	0.060	.	0.099	0.179	1	−0.019	0.049
sd	0.014	0.015	0.017	.	0.015	0.014	0	0.015	0.018
min	0.065	0.157	0.022	.	0.054	0.140	1	−0.052	0.005
max	0.145	0.239	0.121	.	0.134	0.209	1	0.019	0.088
adip	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	−0.126	−0.082	−0.353	−0.130	−0.060	−0.050	−0.019	1	−0.219
sd	0.009	0.006	0.014	0.009	0.010	0.007	0.015	0	0.015
min	−0.147	−0.097	−0.384	−0.155	−0.088	−0.064	−0.052	1	−0.246
max	−0.102	−0.064	−0.309	−0.112	−0.036	−0.035	0.019	1	−0.181
wbbc	FIB	CRP	PAI1	IL6	TNFA	ICAM1	IL10	ADIP	WBCC
mean	0.291	0.319	0.160	0.234	0.058	0.173	0.049	−0.219	1
sd	0.005	0.005	0.008	0.015	0.016	0.009	0.018	0.015	0
min	0.279	0.306	0.142	0.207	0.024	0.150	0.005	−0.246	1
max	0.309	0.333	0.180	0.280	0.099	0.195	0.088	−0.181	1

The average correlations among eight metabolic traits and nine inflammatory markers predict to some extent, especially via factor analyses, which trait combinations are useful and may reflect underlying MetS etiology, out of 130,305 possible trait combinations.

2.1.5. Correlated meta-analysis

Pleiotropic effects can result from a single pleiotropic locus (SNP/gene) affecting different traits, or from a group of alleles at distinct loci (SNPs/genes), but in linkage disequilibrium (statistical nonindependence) [41]. While examples of studies focused on pleiotropy based on published results [42,43], as well as methods on linked pleiotropic loci exist [44,45], our study focuses only on single pleiotropic sites (single SNPs) and the corresponding mapped genes, that associate simultaneously with metabolic traits and inflammatory markers as well as takes advantage of correlated meta-analyses.

We performed correlation analysis of 8 metabolic traits and 9 inflammatory markers, as a premise in identifying useful combinations that may help in discovering genetic pleiotropy. Based on such analysis we had selected 8 trait combinations for follow-up. This large number of results combined requires an unbiased method for meta-analyzing them. When meta-component scans are not independent, it can inflate type-I error, since at each location in the genome, a false-positive finding for one of the scans has an enhanced probability of being a false positive in any correlated scan. Province, and Province and Borecki [31,32] developed a method for correcting bias via a correlated meta-analysis, which only requires the GWAS results and does not need the individual genotype/phenotype data. The basic idea is that for a trait of interest, the vast majority of the genome is under the null hypothesis of no genotype–phenotype association, which is only mildly contaminated with a relatively few SNPs that are under the alternative. Thus, the method performs sampling of GWAS genome via the polychoric correlation estimator [46], (using SAS PROC FREQ). It is the estimate of the N × N correlation matrix, Σ between N scans, that is used to correct the final meta-estimates for this correlation.

In this article, the meta-analyses were based on p-values combinations, which involved the Fisher's 1925 [47] method of combining p-values at each location of the genome [48]. This technique uses the fact that for N scans, $\sum -2\ln(p_i) \sim \chi^2$ with 2n degrees of freedom, so the tail probability provides the meta-analysis p-value. Unfortunately, in the case of correlated GWAS, this sum is no longer distributed as a simple chi-square. Instead, in the correlated meta-analysis method, Province uses an inverse-normal transform, $Z_i = \varphi^{-1}(p_i)$ forming the N dimensional vector $\underline{Z}$ of all Z_is. He then applies the basic theorem of multidimensional statistics that for matrix $\underline{D}$, if $\underline{Z} \sim N(\underline{0},\Sigma)$ then $\underline{D}\,\underline{Z} \sim N(\underline{0},D\Sigma D')$. In particular, when D is a 1 × N vector of all 1's, $SUM(\underline{Z}) = \underline{D}\,\underline{Z} \sim N(0,SUM(\Sigma))$, whose tail probability gives the Z meta-analysis p-value. In this case, for estimating Σ, the SNP p-values are dichotomized across the genome as ($P \le 0.5$; $P > 0.5$). The software was developed in SAS by Province [31] and an interface was built with SAS/InterNet to perform parallel computing of each meta-analysis within the Division of Statistical Genomics, Washington University computing cluster.

2.1.6. Bioinformatics of selected genes

Another approach we used to appraise pleiotropy was searching Gene Entrez of NCBI (http://www.ncbi.nlm.nih.gov/gene/) for genes related to each of the traits studied: "body mass index", "waist circumference", "high density lipoprotein cholesterol", "triglycerides", "insulin", "glucose", "systolic blood pressure", "diastolic blood pressure", "fibrinogen", "C-reactive protein", "plasminogen activator 1", "interleukin 6", "interleukin 10", "intercellular adhesion molecule 1", "tumor necrosis factor alpha", "adiponectin" and "white blood cell counts". Our search was limited only to human, mouse and rat species. Identified genes represent publication evidence of their contribution to a trait based on linkage, association, function, expression etc. All single traits gene lists were merged by gene name and selected for most contributions among metabolic traits and inflammatory markers, selected with a minimum threshold of 8 contributions between the two of them (Supplemental Table 6).

For the same terms, searches were implemented also at www.genome.gov/26525384. These data represent large genome wide studies with at least 100,000 SNPs and with a high statistical significance in the overall (initial GWAS + replication) population [49]. Genes identified as possible candidates were checked via Association Results Browser of dbGaP of NCBI http://www.ncbi.nlm.nih.gov/projects/gapplusprev/sgap_plus.htm. The same database was used to identify genes reported to associate with "metabolic syndrome". Results are reported in Supplemental Tables 7 and 8. The SNPs were checked if they served as eQTLs based on the eQTL NCBI database (http://www.ncbi.nlm.nih.gov/gtex/GTEX2/gtex.cgi).

The importance of gene lists identified was mined by means of GeneGO (http://thomsonreuters.com/products_services/science/systems-biology/) and Literature Lab of ACUMENTA (http://acumenta.com/) software. The GeneGO, enrichment analysis consists of matching gene IDs of possible targets for the "common", "similar" and "unique" sets with gene IDs in functional ontologies in MetaCore, MetaDrug, MetaBase, Specialty modules, and System toxicology. The probability of a random intersection between a set of IDs the size of target list with ontology entities is estimated in p-value of hypergeometric intersection. The lower p-value means higher relevance of the entity to the dataset, which shows in higher rating for the entity. Literature Lab on the other hand, is an interface between experimentally-derived gene lists and scientific literature in a curated vocabulary of 24,000 biological and biochemical terms. It employs statistical and clustering analysis on over 14 million PubMed abstracts (01/01/90 to the present) to identify pathways (809 pathways), diseases, compounds, cell biology and other areas of biology and biochemistry. The analysis engine compares statistically the submitted gene set to 1,000 random gene sets generated on-the-fly to identify term relationships that are associated with the gene set more than by chance alone.

3. Results

3.1. Epidemiological associations between inflammatory markers and MetS

Using data from more than 85,500 participants across 14 cohorts (Table 1.a), we assessed at the phenotypic level the associations between 9 inflammatory markers CRP, FIB, PAI-1, IL-6, IL-10, ICAM-1, WBCC, TNFA and ADIP and MetS. Metabolic traits studied were BMI, WAIST, HDLC, TG, GLUC, INS, SBP and DBP (Supplemental Table 1). The mean age varied from 25 (SD = ±3) years in the CARDIA study to 74 (SD = ±8) years in the Rotterdam Study. These 14 studies capture a range of MetS (NCEP criteria) prevalence, from 2.4% in the baseline measurement of CARDIA-EA to 58.9% in GENOA-EA. The prevalence of MetS and its risk factors, as well as the mean levels of inflammatory markers in individuals with and without MetS, is summarized for two representative studies (the Family Heart Study and the Framingham Heart Study in Fig. 1, and for all cohorts in the Supplemental Figs. 1(a–g)). Overall, when comparing mean levels of inflammatory markers in individuals with MetS to those without, significant differences (passing Bonferroni threshold, $p \le 9.43 \times 10^{-4}$) were observed between the two strata in 85% (45 out of 53) of comparisons. FIB, CRP, PAI-1, ICAM-1, WBCC and TNFA mean levels were higher, whereas ADIP mean level was lower in individuals with MetS. There were also exceptions such as IL-10 (present only in one study), which did not show significant mean differences between individuals with and without MetS.

3.2. Correlations among metabolic traits and inflammatory markers

We calculated the pair-wise correlations between traits measured within individual studies (Supplemental Tables 9–22). The generalization of the within-study trait correlation to a global average correlation

matrix was used to prioritize combinations of metabolic traits and inflammatory markers for subsequent correlated meta-analyses to evaluate the hypothesis of genetic pleiotropic associations between MetS risk factors and inflammatory markers. The estimation of average correlations across studies was approached with two methods. First, we simulated standardized normal variables with mean 0 and variance 1 based on the correlations and sample size (with missing values) of individual studies, because the original data at the participant level were not available (Section 2.1.3). The overall average Pearson pairwise correlations were estimated from 100 replications of simulations with more than 85,500 individuals per replication (Table 2). Second, using Fisher's Z-transformation (Section 2.1.3) we combined original correlations of single studies to an overall average correlation coefficients matrix. The average estimated values of correlation coefficients resulting from the two methods (Table 2 and Supplemental Table 2) were similar. Pertinent and significant correlations between inflammatory markers and metabolic traits were (1) FIB and CRP with all metabolic traits studied; (2) ICAM-1 and TNFA with HDLC and TG; and (3) ADIP and WBCC with WAIST, HDLC, TG and INS.

Additionally, based on the overall studies' average correlations, we built a second batch of simulated data for all traits. These simulations had 100 replications, each trait with a mean 0 and standard deviation of 1 with more than 85,500 individuals per replication and this time with no missing observations. We performed with them factor analyses (Section 2.1.4), which gave us a second opportunity to identify additional priority combinations of traits as shown in the Supplemental Fig. 2. Factor 1 represented a combination of (4) BMI, WAIST, INS, CRP, PAI-1 and weaker contributions of HDLC and TG; (5) weak contributions of BMI and WAIST were associated in Factor 2 with strong contributions of FIB, CRP, IL-6 and WBCC; (6) TG and less so HDLC, contributed along with CRP and WBCC in Factor 4; (7) HDLC and TG with PAI1 and ADIP in Factor 5, and (8) GLUC and INS contributed to Factor 6 along with PAI-1. Supplemental Table 3 shows results of the coefficients of congruence for factors derived across replications (CC, Section 2.1.4). The congruence of Factor 1 across replications was high (CC = 0.99). Factor 3 had only contributions from blood pressure and no noteworthy contributions of inflammatory markers and thus was not considered for follow-up in the correlated meta-analyses. As a result eight trait clusters were selected for correlated meta-analyses.

3.3. Correlated phenotype-GWAS meta-analyses

Finally, we implemented nine correlated meta-analyses (Section 2.1.5), representing eight trait-combinations predicted from Section 3.2, and one including all variables. We utilized GWAS meta-summary-results from individual traits published mainly by large consortia (Table 1.b) for 8 metabolic traits (BMI [23], WAIST [33], HDLC and TG [24], GLUC and INS [20], SBP and DBP [22]), and 6 inflammatory markers (CRP [25], PAI-1 [26], ICAM-1 [28], WBCC [27], ADIP [34] and IL-6 [35]). The significance threshold of meta-analyses was set at $-\log_{10}p \geq 8$. In addition, results were filtered requiring at least one metabolic trait and at least one inflammatory marker had an individual trait significance of $-\log_{10}p \geq 3$. After selecting the lead SNP for each locus fulfilling the above three conditions, 130 unique SNPs remained, each simultaneously associating to at least one metabolic trait and one inflammatory marker (pleiotropic associations per variant). We infer for each SNP the corresponding mapped gene underlying such pleiotropic association (Supplemental Table 4). Of the 130 unique mapped genes, 25 mapped genes were selected as candidates for MetS, because each corresponding SNP showed at least two associations to metabolic traits from our analyses or GWAS literature and at least one association with inflammatory markers (Table 3). The 25 genes represent 15 distinct genomic loci with associations with MetS risk factors and inflammatory markers. A short description of the known functions of these 25 genes is provided in Table 4, and additional evidence is summarized in Table 5, Supplemental Table 5 and Fig. 2, including annotation from the ENCODE by using HaploReg [50] and RegulomeDB [51] software and their additional databases.

As shown in Fig. 2, specific SNPs based on their pleiotropic associations were classified in three main groups. The first group of pleiotropic associations for lipids and inflammation, included a SNP mapped to *MACF1* [52,53] and another SNP mapped to *KIAA0754* on chromosome 1. Both mapped genes associated with HDLC and with WAIST, TG, GLUC and CRP. Furthermore on chromosome 2, a rich strand (~1.2 M bps in length) of 23 contiguous genes, from *TCF23* to *BRE* was associated with TG and CRP. This region contains rs1260326 of *GCKR*, which encodes a missense change Leu446Pro, associated with both TG [24] and CRP [25]. Another independent group of SNPs on chromosome 2 mapped to genes *GRB14* and *COBLL1*, positioned about 4.7 K bps apart and each associated with HDLC, TG, PAI-1 and ADIP. A SNP near *LOC646736* (~23 K bps), showed pleiotropic associations with HDLC, TG and ADIP. The *LOC646736* is an uncharacterized gene on chromosome 2 located ~528 K bps from the *IRS1* gene. Intronic variants of *BAZ1B*, *BCL7B*, *TBL2* and *MLXIPL* (7q11.23) were associated with TG, HDLC and CRP. An untranslated variant of *LPL* (8p22) was associated with HDLC, TG and CRP. *TOMM40* (19q13) showed similar phenotypic association patterns. Rs10808546 about 45 K bps from neighboring *TRIB1* (8q24.13) was associated with TG, HDLC [24], ADIP and PAI-1. An intron SNP of *ZNF664* (12q24.31) was associated with TG, HDLC and ADIP.

The second group with pleiotropic associations for adiposity/obesity and inflammation included *TFAP2B* (6p12), where its corresponding SNP was significantly associated with BMI, WAIST and CRP; selected SNPs corresponding to *HECTD4* (12q24.13) and *PTPN11* (12q24) were associated with ICAM-1, DBP, SBP, HDLC, BMI and WAIST, while an intron variant of *FTO* (16q12.2) was associated with BMI, WAIST, CRP and INS.

The third group of mapped genes showed pleiotropic associations for adiposity/obesity, lipids and inflammation. Among them were a missense variant rs13107325 of *SLC39A8* (4q22–q24), that associated with HDLC [24], BMI, ADIP, SBP, DBP and WAIST. The same SNP was previously reported in association with blood pressure, hypertension (HTN) [54], and BMI [23]. Three SNPs mapping respectively to *NELFE*, *SKIV2L* and *STK19* (6p21) associated each to TG, BMI, WAIST, SBP, PAI-1 and WBCC. They are located in the class III region of the major histocompatibility complex of chromosome 6, close to the *C2* gene. An intron SNP of *PDXDC1* (16p13.11) was associated with ADIP, WAIST and TG. Finally, rs6567160 mapped to *MC4R* (18q22) was associated with BMI, WAIST, CRP, HDLC and TG.

3.4. Bioinformatics analyses

We searched the literature for all sources of publications that associated genes with effects on both metabolic traits and inflammatory markers. If the same gene is published to affect different traits then it supports the pleiotropy hypothesis. First, keyword searches based on single trait labels (Section 2.1.6) using Gene Entrez of NCBI produced a list of 770 genes that had a relationship with at least one of the eight metabolic traits and at least one of the nine inflammatory markers. Of these, 48 putative pleiotropic genes were ranked with a total number of ≥8 associations with metabolic traits and inflammatory markers keyword searches, sourced from three species: human, mouse and/or rat (Supplemental Table 6). Highest ranked for possible pleiotropic effects were the *ADIPQ*, *PPARG* and *LEP* genes. Of this list through literature search, *APOE*, *FTO*, *MMP9* and *VEGFA* overlapped with our 130 pleiotropic gene list (Supplemental Table 4).

A second source of pleiotropic candidate genes was selected from previous GWAS literature (Section 2.1.6 and Supplemental Table 7). Eleven genes in this list showed association with a single inflammatory marker, but with up to four associations with metabolic traits. Among them, *GCKR* was associated with four metabolic traits and CRP, while *TRIB1* and *TOMM40* were associated with HDLC, TG and ADIP and CRP,

Table 3

Meta-analyses results of 9 classes of trait-combinations. Note: Selected are best SNPs per gene with up to three possibilities, within a gene, up to 5 KB from the nearest gene or beyond 5 KB to the nearest gene. To be selected a SNP had to fulfill the following conditions: meta-analysis $-\log_{10}p \geq 8$ and at least one metabolic trait and one inflammatory marker with $-\log_{10}p \geq 3$. The table represents SNPs that can be considered as contributors to MetS. They pass meta $-\log_{10}p \geq 8$. SNPs that pass or reach a threshold of $-\log_{10}p \geq 3$ are shown in yellow color, SNPs that pass or reach a threshold of $-\log_{10}p \geq 8$ for single trait associations are shown in orange color, and green indicates SNPs that might show some protective effect against MetS (see Discussion for clusters of ADIP and HDLC). Abbreviations: rs — rsname, chrom — chromosome, position in bps, meta_nlog10p — meta-analysis $-\log_{10}p$, BMI, WAIST, HDLC, TG, GLUC, INS, SBP, DBP, CRP, PAI1, IL6, ICAM1, ADIP, and WBCC represent $-\log_{10}p$ values for each trait association to a SNP, hugo — gene symbol, role — SNP's role, diffPosNearGene is a distance in bps from the start or end SNP of the closest mapped gene, while 0 distance when within a gene, newhugo — the closest mapped gene to the reported SNP; a particular SNP is marked with ()_beyond when more than 5 K bps distant from its mapped gene.

No	Trait combination	rs	Chrom	Position	meta_nlog10p	BMI	WAIST	HDLC	TG	GLUC	INS	SBP	DBP	CRP	PAI1	IL6	ICAM1	ADIP	WBCC	hugo	role	diffPosNearGene	newhugo
1	1. bwhtgisd_rp	rs1537817	1	39639653	17.71	1.52	3.24	8.94	5.14	2.99	1.28	2.47	1.93	6.33						MACF1	intron–variant	0	MACF1
2	1. bwhtgisd_rp	rs3768302	1	39880319	15.73	1.15	2.72	8.72	4.90	2.95	0.89	2.20	1.65	6.56						KIAA0754	utr–variant–3–prime	0	KIAA0754
3	6. ht_rpcc	rs1260326	2	27730940	78.71			1.11	132.25					42.26					0.23	GCKR	missense	0	GCKR
4	7. ht_i1ip	rs10184004	2	165508389	18.21			6.98	9.76						2.54			4.52				28106	(GRB14)_beyond
5	7. ht_i1ip	rs10195252	2	165513091	18.33			7.03	9.79						2.65			4.44				–27709	(COBLL1)_beyond
6	7. ht_i1ip	rs2943634	2	227068080	15.59			8.63	7.29						0.96			5.22				22841	(LOC646736)_beyond
7	9. bwhtgisdt2d_rpi1l6m1ipcc	rs13107325	4	103188709	13.27	6.86	3.16	10.14	1.82	0.18	0.40	3.91	4.18	0.36	0.48		1.87	4.13	0.15	SLC39A8	missense	0	SLC39A8
8	9. bwhtgisdt2d_rpi1l6m1ipcc	rs419788	6	31928799	12.72	4.48	2.52	0.07	13.56	0.14	0.71	3.25	0.82	1.65	3.07	0.83	1.06	1.20	3.71	NELFE	upstream–variant–2KB	0	NELFE
9	9. bwhtgisdt2d_rpi1l6m1ipcc	rs437179	6	31929014	12.50	4.41	2.54	0.11	13.46	0.20	0.64	3.28	0.84	1.49	2.89	0.83	1.09	1.07	3.24	SKIV2L	missense	0	SKIV2L
10	9. bwhtgisdt2d_rpi1l6m1ipcc	rs389883	6	31947460	13.49	4.43	2.46	0.24	14.40	0.19	0.90	3.74	0.99	1.43	3.05		0.94	1.16	3.06	STK19	intron–variant	0	STK19
11	5. bw_rpl6cc	rs3857599	6	50938247	15.42	13.58	10.21							3.64					0.54			122468	(TFAP2B)_beyond
12	6. ht_rpcc	rs7811265	7	72934510	37.67			5.92	58.04					7.25					0.70	BAZ1B	intron–variant	0	BAZ1B
13	6. ht_rpcc	rs13233571	7	72971231	35.49			8.54	57.03					7.55					0.07	BCL7B	intron–variant	0	BCL7B
14	6. ht_rpcc	rs11974409	7	72989390	35.79			5.49	57.90					6.94					0.51	TBL2	intron–variant	0	TBL2
15	6. ht_rpcc	rs17145750	7	73026378	36.94			6.82	57.80					6.33					0.56	MLXIPL	intron–variant	0	MLXIPL
16	6. ht_rpcc	rs3289	8	19823192	32.66			26.70	18.94					3.60					1.44	LPL	utr–variant–3–prime	0	LPL
17	7. ht_i1ip	rs10808546	8	126495818	51.41			18.20	53.42						2.94			4.60				44737	(TRIB1)_beyond
18	9. bwhtgisdt2d_rpi1l6m1ipcc	rs653178	12	112007756	14.55	3.83	3.48	5.80	0.69	0.36	0.26	3.43	6.71	0.44	0.43	2.12	16.50	0.02	1.60	ATXN2	intron–variant	0	ATXN2
19	9. bwhtgisdt2d_rpi1l6m1ipcc	rs11066188	12	112610714	9.16	4.01	3.62	2.69	0.12	0.35	0.13	3.52	5.90	0.33	0.07		11.36	0.17	1.93	HECTD4	intron–variant	0	HECTD4
20	9. bwhtgisdt2d_rpi1l6m1ipcc	rs11066320	12	112906415	8.97	3.83	3.24	2.70	0.24	0.34	0.06	3.70	5.75	0.44	0.22		9.41	0.28	1.19	PTPN11	intron–variant	0	PTPN11
21	7. ht_i1ip	rs12310367	12	124486678	15.55			9.51	7.92						0.14			7.94		ZNF664	intron–variant	0	ZNF664
22	3. whti_ipcc	rs4985155	16	15129459	8.23		5.00	1.66	4.92		0.58							4.11	0.22	PDXDC1	intron–variant	0	PDXDC1
23	4. bwi_rpi1	rs1558902	16	53803574	60.99	61.69	49.38				4.12			5.65	1.41					FTO	intron–variant	0	FTO
24	1. bwhtgisd_rp	rs6567160	18	57829135	24.58	21.74	18.08	7.91	4.75	0.34	1.79	0.75	0.64	3.82								–208947	(MC4R)_beyond
25	6. ht_rpcc	rs2075650	19	45395619	67.63			15.96	18.88					86.52					0.16	TOMM40	intron–variant	0	TOMM40

Table 4
A summary of 25 MetS candidate genes functions.

No[a]	Gene	Location	Function (references)	Annotating marker	Allele (frequency)
Group 1. Pleiotropic genes for lipids and inflammation					
1	MACF1	1p32–p31	"Microtubule-actin crosslinking factor 1"; Produces a protein that forms bridges between different cytoskeletal elements, by stabilizing and guiding microtubule growth along actin filaments. An alternative spliced form associates with the Golgi apparatus.	rs1537817	T (0.2156)
2	KIAA0754	1p34.3	An uncharacterized gene.	rs3768302	G (0.2859)
3	GCKR	2p23	"Glucokinase (hexokinase 4) regulator"; GCKR's protein is a regulatory protein that inhibits glucokinase in liver and pancreatic islet cells by binding non-covalently to form an inactive complex with the enzyme.	rs1260326	T (0.3963)
4	GRB14	2q22–q24	"Growth factor receptor-bound protein 14", which likely produces an inhibitory effect on insulin receptor signaling,	rs10184004	T (0.4214)
5	COBLL1	2q24.3	"Cordon bleu"; a conserved gene involved in neural tube formation.	rs10195252	C (0.4205)
6	LOC646736	2q36.3	An uncharacterized gene.	rs2943634	A (0.3428)
12	BAZ1B	7q11.23	"Bromodomain adjacent to zinc finger domain, 1B"; The bromodomain is a structural motif characteristic of proteins involved in chromatin-dependent regulation of transcription. This gene is deleted in Williams–Beuren syndrome.	rs7811265	G (0.191)
13	BCL7B	7q11.23	"B-cell CLL/lymphoma 7B"; This gene is located at a chromosomal region commonly deleted in Williams syndrome. This gene is highly conserved from C. elegans to human.	rs13233571	T (0.1209)
14	TBL2	7q11.23	"Beta-transducin like 2"; involved in regulatory functions. This protein is possibly involved in some intracellular signaling pathway. This gene is deleted in Williams–Beuren syndrome.	rs11974409	G (0.1906)
15	MLXIPL	7q11.23	"Helix–loop–helix leucine zipper transcription factor of the Myc/Max/Mad superfamily"; This protein forms a heterodimeric complex and binds and activates, in a glucose-dependent manner, carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes. The gene is deleted in Williams–Beuren syndrome.	rs17145750	T (0.1496)
16	LPL	8p22	"Lipoprotein lipase"; is expressed in heart, muscle and adipose tissues. Its main functions are the hydrolysis of triglycerides of circulating chylomicrons and very low density lipoproteins, and to serve as a ligand or bridging factor for receptor-mediated lipoprotein uptake. The apolipoprotein APOC2, acts as a coactivator of LPL in the presence of lipids on the luminal surface of vascular endothelium, whereas ANGPTL4 expression in adipose tissue as induced by fasting is proposed as an inhibitor of LPL in adipose tissue to reroute fat from adipose tissue to other tissues.	rs3289	C (0.028)
17	TRIB1	8q24.13	"Tribbles pseudokinase 1";	rs10808546	T (0.4425)
21	ZNF664	12q24.31	"Zinc finger protein 664";	rs12310367	G (0.3367)
25	TOMM40	19q 13	"Translocase of outer mitochondrial membrane 40 homolog (yeast)"; channel-forming subunit of the translocase of the mitochondrial outer membrane (TOM) complex that is essential for protein import into mitochondria.	rs2075650	G (0.1533)
Group 2. Pleiotropic genes for adiposity/obesity and inflammation					
11	TFAP2B	6p12	"Transcription factor AP-2 beta"; TFAP2B is a transcription factor that stimulates cell proliferation.	rs3857599	A (0.1734)
19	HECTD4	12q24.13	"HECT domain containing E3 ubiquitin protein ligase 4";	rs11066188	A (0.4152)
20	PTPN11		"Protein tyrosine phosphatase, non-receptor type 11"; PTPN11 produces a protein tyrosine phosphatase non-receptor 11 involved in cell growth, differentiation, and mitotic cycle.	rs11066320	A (0.421)
23	FTO	16q12.2	"Fat mass and obesity associated"; Studies in mice and humans indicate a role in nervous and cardiovascular systems and a strong association with body mass index, obesity risk, and type 2 diabetes	rs1558902	A (0.4163)
Group 3. Pleiotropic genes for adiposity/obesity, lipids and inflammation					
7	SLC39A8	4q22–q24	"Solute carrier family 39, member 8"; a solute carrier with structural characteristic of a zinc transporter. It is found in the plasma membrane and mitochondria, and functions in the cellular importation of zinc at the onset of inflammation.	rs13107325	T (0.0748)
8	NELFE	6p21.3	"Negative elongation factor complex member E"; Represses RNA polymerase II transcript elongation; Localizes to the major histocompatibility complex (MHC) class III region on chromosome 6.	rs419788	T (0.2954)
9	SKIV2L	6p21	"Superkiller viralicidic activity 2-like"; DEAD box proteins, characterized by the conserved motif Asp-Glu-Ala-Asp (DEAD), are putative RNA helicases. Some members of this family are believed to be involved in embryogenesis, spermatogenesis, and cellular growth and division.	rs437179	A (0.2956)
10	STK19	6p21.3	"Serine/threonine kinase 19"; it is possible that phosphorylation of this protein is involved in transcriptional regulation. This gene localizes to the major histocompatibility complex (MHC) class III region on chromosome 6	rs389883	G (0.2954)
18	ATXN2	12q24.1	"Ataxin 2"; The autosomal dominant cerebellar ataxias are a heterogeneous group of neurodegenerative disorders characterized by progressive degeneration of the cerebellum, brain stem and spinal cord.	rs653178	C (0.4687)
22	PDXDC1	16p13.11	"Pyridoxal-dependent decarboxylase domain containing 1";	rs4985155	G (0.3319)
24	MC4R	18q22	"Melanocortin 4 receptor"; A membrane-bound receptor and member of the melanocortin receptor family. Defects in this gene are a cause of autosomal dominant obesity.	rs6567160	C (0.2381)

[a] The corresponding number matches with Table 3 order number (in Table 3 this corresponds with ordering genes by chromosome and position).

Table 5
A short summary of additional supportive findings for the 25 MetS pleiotropic candidates.

Group 1: Pleiotropic genes for lipids and inflammatory markers

- The MACF1 was also associated with T2D [72]. Recently, Fassett et al. [73] using inducible cardiac-specific MCF1 knockout mice concluded this gene works as a stress induced regulator of cardiomyocyte microtubule distribution and is important for ventricular adaptation to hemodynamic overload. The GCKR rs1260326 was associated with T2D risk, by changing the ability of GCKR to sequester glucokinase in the nucleus of hepatocytes [74], and with hepatic fat accumulation along large VLDL and TG levels in obese youth [84]. Rees et al. [74], suggested that leucine allele elevates hepatic glucose uptake and disposal by increasing active cytosolic GCK, which would increase hepatic lipid biosynthesis. Another GCKR SNP was associated with serum albumin [59], decreased levels of amino acids alanine and isoleucine and elevated levels of glutamine [85], with liver enzyme gamma-Glutamyltrasferase [65], and platelet count [79]. GCKR was associated with serum calcium [81]. GCKR has already been proposed as a candidate for MetS for its significant associations with qualitative bivariate TG-BP and WC-TG [80]. The rs2303369, neighboring GCKR and an intron of fibronectin type III (FNDC4) was associated significantly with menopause [86]. The GRB14 protein has a pleckstrin homology domain, a C-terminal Src homology 2 (SH2) domain, and an intervening ~45 residues known as BPS. GRB14 and its family members GRB7 and GRB10 are recruited by a number of receptor tyrosine kinases [78]. This recruitment is facilitated via phosphotyrosine binding the SH2 domain, while the INS and IGF1 receptors are recruited by the BPS region [75]. Cooney et al. [77] noticed an improved glucose tolerance and an enhanced insulin-induced signaling in muscle and liver, but not in adipose tissue in a male mice deficient for Grb14 (−/−). They proposed that Grb14 was a negative regulator, tissue specific for insulin signaling. In a gene expression study, Grb14 expression was elevated in adipose tissue of both ob/ob mice and Goto-Kakizaki (non-obese T2D) rats [75]. Our meta-analyses results add to the importance of GRB14, which can be viewed as an inhibitor of the insulin receptor and therefore as affecting insulin signaling. The COBLL1 [76] was associated with T2D [72]. Adjacent to this gene toward GRB14 are a number of SNPs that were associate with T2D [134], TG [24] and HDLC [24]. Albrechtsen et al. [72]. showed that COBLL1 expresses in pancreatic islets and kidney, and to some degree in skeletal muscle, liver and adipose tissue. They stipulated COBLL1 variants may influence expression of nearby GRB14 to change insulin sensitivity. The LOC646736 rs2943634 was associated with coronary disease [83] and T2D [82]. Downstream (~47 K bps) from this SNP, an intron of LOC646736 was associated with T2D [98]. Upstream of our meta-SNP, a few SNPs associates with TG [24], with adiposity [94], and with ADIP [34]. The LPL is significantly associated with TG and HDLC (Several studies confirm these associations). LPL is part of glycerolipid metabolism pathway (map00561, kegg.jp), involved in free fatty acids production, and is also a member of PPAR signaling pathway (map03320, kegg.jp). The TRIB1 is reported in associations with TG, HDLC, LDLC [24], with alkaline phosphatase and alanine transaminase [65], with ADIP_[34], with Crohn's Disease [101], with bivariate qualitative combinations of HDLC-TG and TG-BP [80]. Recently Akira et al. [100] working with *Trib1*(−/−) mice demonstrated that mice lacking Trib1 in hematopoietic cells exhibited severe lipodystrophy due to increased lipolysis, while in a high-fat diet, mice exhibited hypertriglyceridemia, insulin resistance, together with increased proinflammatory cytokine production. They suggested, that Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident anti-inflammatory-like macrophages. The rs10808546 positioned about 45 K bps from TRIB1 is located in a DNAase mark often found in active regulatory elements. The ZNF664 associates with visceral adipose tissue adjusted for BMI and with visceral adipose tissue/subcutaneous adipose tissue ratio for women [103]. TOMM40 SNPs are in linkage disequilibrium with APOE SNPs (HapMap LD plot not shown). TOMM40 is positioned at the side of the cluster APOE/APOC4/APOC2 and was associated with Alzheimer's disease [104,114], low density lipoprotein cholesterol (LDLC) and HDLC [87] and CRP [87,113]. The rs2075650 of TOMM40 is part of three signatures of promoter histone marks, part of enhancer histone markers in 6 cell types, it can be involved in a DNase signature, and is part of 8 changed motifs, among them sterol regulatory element binding transcription factor (SREBP).

Group 2: Pleiotropic genes for adiposity/obesity and inflammation

- An intron of TFAP2B, was associated with the effects of dietary fat intake on weight loss and waist reduction [117]. A few other SNPs of TFAP2B associated significantly with BMI [23], adiposity [108] and with a qualitative bivariate WAIST-GLUC combination [80]. The PTPN11 was associated with platelet counts [115], with TG [120], and with carotid arteries [112]. While FTO contributes to the regulation of the global metabolic rate, energy expenditure, energy homeostasis, regulation of body size and body fat accumulation, its exact function is not known. Other SNPs of FTO were associated with BMI [23], body weight [119], adiposity [94], WAIST [105], with T2D [121] and less so with factor 1 and factor 2 of MetS risk factors [63].

Table 5 (*continued*)

Group 3: Pleiotropic genes for adiposity/obesity, lipids and inflammation

- The SLC39A8 protein is found in the plasma membrane and mitochondria, and functions in the cellular transport of zinc at the onset of inflammation. SLC39A8 is a negative regulator of NF-kB and functions to negatively regulate proinflammatory responses through zinc-mediated down-modulation of IkB kinase (IKK) activity [109]. SLC39A8 and SLC39A14 are regulated by IL-6 dependent signaling in the liver [110]. In addition, rs230487, which is closer to NFKB1 than SLC39A8 was associated with tissue Plasminogen activator [120]. Liu et al. [109] proposed that SLC39A8 and SLC39A14 are important zinc transporters that channel zinc in a tissue-specific manner to fundamentally important intracellular checkpoints, which help to coordinate and balance host defense. The NELFE, SKIV2L and STK19 position in the class III region of the major histocompatibility complex of chromosome 6. The three genes are likely involved in transcription regulation and have been found to be associated with Macular Degeneration and Lupus Erythematosus, and rs2072633, an intron of CFB — complement factor B, (but only 286 bps from NELFE gene) [106] being associated with Multiple Sclerosis. The association of PDXDC1 with ADIP may indicate that its pleiotropic effect could have protective contributions for inflammation and MetS. Based on the ENCODE information the rs4985155 is located in a transcription factor binding site and corresponds to a DNase peak (based on HaploReg [50] and regulomeDB [51] software). The rs4500751, (chr16:15140211) mapped at NTAN1 about 10.7 K bps from our PDXDC1 meta-SNP, associated with absolute plasma levels and proportions of the phospholipid species with important roles in cell survival and inflammation [102]. Other SNPs associated with blood metabolite concentration [118], and with phospholipids levels in plasma [107]. The MC4R is a member of melanocortin family. The melanocortins are involved in pigmentation, energy homeostasis, inflammation, immunomodulation, steroidogenesis and temperature control. Staubert et al. [116] found a strong correlation between positional conservation and the functional relevance of missense, nonsense, and frame-shifting mutations ofMC4R affecting 60 amino acid positions. The mostly heterozygous (dominant) occurring MC4R mutations are implicated in 1–6% of early-onset or severe adult obesity cases. Some of the GWAS findings indicated that MC4R was associated with BMI [23,33], obesity [111], body height [122], with body weight [119], WAIST [88], and with HDLC [24].

respectively. With the exception of *CSMD1*, the remaining ten genes (*GCKR*, *IRS1*, *LYPLAL1*, *TRIB1*, *APOE*, *TOMM40*, *PPP1R3B*, *PEPD*, *BCL7B*, *TMEM18*) are present in the list of 130 pleiotropic candidate genes of metabolic traits and inflammatory markers.

A third source of pleiotropic candidate genes was the gene search for "metabolic syndrome" via dbGaP Association Results Browser, which includes findings of the Catalog of Published Genome-Wide Association Studies (Section 2.1.6). This search yielded 30 MetS candidate genes (Supplemental Table 8). The overlap: *GCKR*, *C2orf16*, *ZNF512*, *TFAP2B*, *MLXIPL*, *LPL*, *TRIB1*, *MTNR1B*, *FTO*, *TOMM40*, represents 33% of the Browser MetS list and 7.7% of our 130 gene pleiotropic list (Supplemental Table 4).

GeneGO database pathway analysis was performed for our 130 candidate pleiotropic genes. The pathway map of "*ZNF202* role in gene expression in atherosclerosis", was enriched for genes affecting lipid metabolism ($p = 7.0 \times 10^{-8}$), while less significant p-values were for other pathways. For process networks, the most common were those related to inflammation. Since HLA genes are quite enriched in these pathways, removal of 7 genes, whose names started with HLA, produced a list of 123 pleiotropic candidate genes. The pathway maps remained similar as above, however process networks changed to "Complement system" (Inflammation, $p = 5.7 \times 10^{-4}$), and "Blood vessel morphogenesis" (Development, $p = 1.2 \times 10^{-3}$). For the disease classification, GeneGO reports the top ranking diseases as "Metabolic Syndrome" ($p = 1.2 \times 10^{-12}$, *TRIP8*, *BMAL1*, *GCKR*, *C2orf16*, *LPL*, *MMP-9*, *HNF4-alpha*, *NTPBP*, *APOE*, *TRIPs*, *TFAP2A*, *ZNF512*, *VEGF-A*, *AP-2B*, *MC4R*, *Notch*, *RGPR*, *Galpha(s)-specific peptide GPCRs*, *FTO*, *HNF4*, *CCDC121*), Obesity ($p = 6.1 \times 10^{-11}$), "Coronary disease" ($p = 1.6 \times 10^{-8}$), "Macular degeneration" ($p = 3.7 \times 10^{-8}$) and T2D ($p = 7.5 \times 10^{-8}$). In the GO processes, "Glucose homeostasis" ($p = 3.0 \times 10^{-9}$), "Positive regulation of vascular permeability" ($p = 8.8 \times 10^{-9}$) and "Regulation of insulin secretion" ($p = 4.0 \times 10^{-7}$) were ranked at the top.

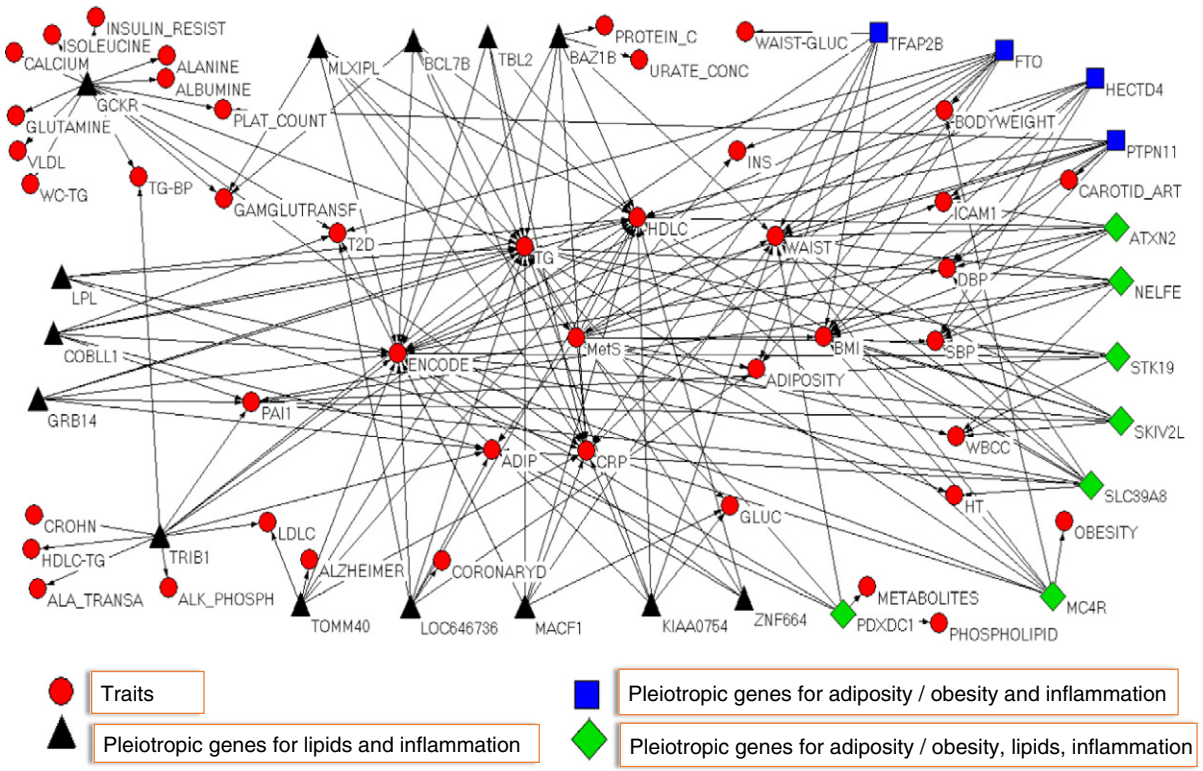

Fig. 2. A network of 25 pleiotropic genes with putative contributions to MetS, including inflammation. Note: In the figure they connect by GWAS phenotypic evidence and whether selected SNPs show any regulatory features based on the ENCODE database as implemented via HaploReg [50]/RegulomeDB [51] software. All phenotypic labels correspond to associations reported in the Results, Discussion, Table 5 and Supplemental Table 5.

The following gene list *GCKR*, *TFAP2B*, *MLXIPL*, *LPL*, *TRIB1*, *FTO*, and *TOMM40* represents 23% of Browser MetS list and 28% of our 25 MetS pleiotropic candidates (Table 3). Bioinformatic analysis using GeneGO database for our 25 MetS candidate genes shows that only a few contribute to the GeneGO Canonical pathway maps. *PTPN11* and *GRB14* are up-regulated, part of the "Development Angiopoietin Tie2 signaling" (enrichment $p = 2.4E-04$), conveying anti-inflammatory action. *PTPN11* is part of six other pathways, while *LPL* is part of three pathways. GeneGO enrichment analysis ranked as the top diseases "Metabolic Syndrome" ($p = 9.0 \times 10^{-7}$); "Obesity" ($p = 8.5 \times 10^{-7}$); and "Insulin Resistance" ($p = 5.6 \times 10^{-7}$). From our list, some of the genes also have been studied for pharmacologic applications. *LPL* is a therapeutic drug target for ibrolipim (activation) and gemfibrozil (activation), while *MC4R* is a target for bremelanotide (activation) and *PTPN11* is a target for stibogluconate (inhibition).

Using the Literature Lab software of ACUMENTA Biotech for an automated literature interrogation [55], the same list of 25 genes showed association, compared with 1000 random sets of genes, for overnutrition ($p = 0.0039$), obesity ($p = 0.0041$), nutrition disorders ($p = 0.0053$), heart valve diseases ($p = 0.0112$), and fatty liver ($p = 0.0124$). The contributing genes in these disease-MeSH term clusters, ranked by the number of the corresponding publications, were for overnutrition: *MC4R* (46.3%), *FTO* (42.4%), *LPL* (10.4%) and *MLXIPL* (0.6%); similar genes were in ranking order for obesity and nutrition disorders; for heart valve diseases *BAZ1B* (47.0%), *PTPN11* (37.5%), *TBL2* (7.7%), and *BCL7B* (6.6%); and for fatty liver *MLXIPL* (89.5%), *LPL* (8.0%) and *GCKR* (1.8%).

4. Discussion

This is the first time that a large sample of more than 85,500 participants with 8 metabolic traits and 9 inflammatory markers is analyzed together with the purpose of understanding relationships of inflammatory markers and MetS. Mean levels of inflammatory markers FIB, CRP, PAI-1, ICAM-1, WBCC and TNFA were higher, while mean ADIP level was lower in individuals classified with MetS compared to those without. These differences reached statistical significance. We explored the pairwise average correlations of all traits over all 14 studies. Correlation estimates and factor analyses yielded eight trait-combinations out of 130,305 possible combinations between metabolic traits and inflammatory markers, which may reflect some of the genetic correlations.

This is also the first time that 8 metabolic traits and 6 inflammatory markers mainly from large consortia meta-analyses are used to search for pleiotropic associations between MetS and inflammation. The analyses yielded 130 top ranked mapped genes with putative pleiotropic associations among metabolic traits and inflammatory markers. Twenty-five variants with pleiotropic associations, each mapped by a single gene, were considered as contributors to MetS per se. We considered MetS candidate genes to be the ones associated with two or more MetS risk factors (from our study and GWAS literature), and with one or more inflammatory markers.

Based on these analyses we infer that a pleiotropic genetic architecture exists and contributes to MetS. But what exactly do we see as pleiotropy at the gene level? Here we focus on a cluster of genes located on 7q11.23. At first glance, genes *BAZ1B*, *BCL7B*, *TBL2* and *MLXIPL*, show pleiotropy by similarly associating TG, HDLC and CRP. A few SNPs of *BAZ1B* were associated with TG [56], protein C [57], and serum urate concentration [58]. *BCL7B*'s SNPs were associated with CRP [25] and with gamma-Glutamyltransferase [59]. *TBL2* was associated with TG [24,60,61] and with HDLC [24]. *MLXIPL* was associated significantly with very low density lipoprotein (VLDL) [62], with MetS [63], with TG [64], and with gamma-Glutamyltransferase [65] (Table 5 and Supplemental Table 5). Deletions of the four above contiguous genes have been identified as causing a Williams–Beuren syndrome, a multisystem developmental disorder, where 75% of cases show severe

GLUC intolerance [66]. *BAZ1B* and *MLXIPL* may serve as transcription factors. The rs17145750 of *MLXIPL*, based on regulomeDB shows some minimal regulatory signature, and from HaploReg software affects a PPAR motif [50]. The rest of the selected SNPs also have some minimal regulatory properties. The majority of the SNPs in the four genes are under two overlapping *linkage disequilibrium* blocks (HapMap figure not shown). It has been reported that *MLXIPL* protein forms a heterodimeric complex and activates, in a glucose-dependent manner, carbohydrate response element (ChoRE) motifs in the promoters of triglyceride synthesis genes. Thus, *MLXIPL* plays a critical role in systemic glucose metabolism, by converting excess carbohydrates to TG by way of de novo lipogenesis [66–68]. Recently, Herman et al. [69] showed in mice that *GLUT4*, officially known as *SLC2A4* (known to be used by insulin for stimulating glucose uptake), regulates the expression of *MLXIPL*. Donnelly et al. [70] studied 9 non-alcoholic fatty liver disease participants (with excess liver TG) and showed that about 26% of TG in the liver was result of de novo lipogenesis, 59% from serum nonesterified fatty acids, 15% from diet, and a similar pattern of isotope labeling in VLDL. Thus, concluding that de novo lipogenesis contributes to the accumulation of hepatic fat. Jeong et al. [71], studied expression of *MLXIPL* using ChIP-seq and identified 14 genes as direct targets that affect the paths from GLUC to TG. They also proposed that *MLXIPL* is an activator and repressor based on gene expression patterns of target genes. The role of *MLXIPL* is complex, because in C57BL/6 mice, global deficiency of *MLXIPL* leads to insulin resistance [67], while in obese mouse with *ob*/*ob* background (leptin deficiency) [67] leads to improved hepatic steatosis and improved insulin resistance. Moreover, Benhamed et al. [66] proposed that *MLXIPL* in the mouse liver raises beneficial lipid species. Thus, the pleiotropic associations of *MLXIPL* are complex and context-dependent.

Our findings are supported by additional GWAS results for several genes of three major pleiotropic groups presented in Fig. 2. A comprehensive GWAS and functional evidence is reported in Tables 4, 5 and Supplemental Table 5 as evidence supporting our findings grouped by pleiotropic genes for 1) lipids and inflammation, 2) adiposity/obesity and inflammation, and 3) lipids, adiposity/obesity and inflammation [12,24,34,59,63–65,72–122]. The power achieved by our study is owing to the use of the world's largest GWAS meta-analyses available (Table 1.b). Because results originate from different consortia, it is possible that studies included may overlap subjects for different traits. However, the approach of correlated meta-analysis we use corrects results if such correlation is present (Section 2.1.5). Previous studies have shown that risk of MetS, is influenced by genes that affect individual MetS risk factors [30,63].

An appealing characteristic of the 130 pleiotropic candidates (Supplemental Table 4) is that several mapped genes are particularly associated with adiponectin and HDLC. Studies have shown that HDLC is a critical risk factor for coronary heart disease. In four studies, an increase by 1 mg/dL in HDLC associated with 2–3% decrease in coronary heart disease risk [123]. Large analyses, also support the importance of HDLC measurement in the risk assessment of heart disease [124,125]. In parallel, increased levels of adiponectin are of interest. For example, Ye and Scherer [126] summarized effects of adiponectin by reviewing either recombinant adiponectin protein, or endogenously its overproduction. In adipose tissue, adiponectin lowers inflammation and increases glucose uptake, fat storage and adipogenesis; in muscle induces an increased fatty acid oxidation; in heart decreases injury and apoptosis; in endothelium decreases oxidative stress and increases angiogenesis and function; in liver increases insulin sensitivity and lowers gluconeogenesis and lipogenesis; and in macrophages increases insulin sensitivity and lowers inflammation. Thus it remains to be investigated, if SNPs with pleiotropic associations to the two phenotypes HDLC and adiponectin are flagging any anti-inflammatory and/or MetS protective effects from these genes (*LYPLAL1*, *GRB14*, *COBLL1*, *STAB1*, *NT5DC2*, *FAM13A*, *SLC39A8*, *ARL15*, *VEGFA*, *HCAR2* [127], *ZNF664*, *CMIP* [128], and *PEPD* [120,129,130]).

In the list of 130 pleiotropic genes, a few special patterns emerged. The SNPs reported in Supplemental Table 5 closer to *LOC646736* and a little more distant to *IRS1* gene appear not to be eQTLs of *IRS1* based on the NCBI database (Section 2.1.6). Co-localization might relate with evolutionary functional importance, which is observed in our data for gene clusters. For example, a missense SNP (rs1260326, T = 0.3963) of *GCKR* associated with similar traits as rs1919127 (C = 0.2647) a missense of *C2orf16*, also as rs23844656 (G = 0.2642), an intron of *ZNF512* and rs13002853 (G = 0.2593) a variant of *CCDC121*; another cluster was for *DNAH10*, *CCDC92*, and *ZNF664* on chromosome 12, and for *HNF4A*, *PLTP*, *PCIF1*, *ZNF335* and *MMP9* on chromosome 20. Such clustering patterns are similar to a pattern previously reported on chromosome 11 for *APOA5*, *ZNF259*, and *BUD13*, where a zinc finger protein probably controls the transcription of nearby genes [80]. It is possible that neighboring gene-variants produce similar results in the associations, because of conserved haplotypes. In the 130 pleiotropic genes, 11 transcription factors (*HEYL*, *SEC16B*, *GTF3C2*, *ZNF512*, *GTF2H4*, *TFAP2B*, *BAZ1B*, *MLXIPL*, *ZNF664*, *MED24*, *HNF4A* and *ZNF335*) represent about 8.5% of the list. Vaquerizas et al. [131] reported 1,391 high confidence loci that encode transcription factors, about 6% of the total of human protein coding genes. Thus the 130-gene list shows patterns that might be common for function conservation. Another feature observed by comparison of 130 pleiotropic candidate genes with the 30 MetS candidate genes (Supplemental Table 8) was that, although *APOA5* and its cluster, as well as *CETP*, *LIPC*, *GALNT2* involved in lipid metabolism are considered contributors to MetS, based on our results they appear not associated directly with inflammation.

The present results suggest that pleiotropic genes play a role in MetS. About two-thirds of our 25 MetS pleiotropic candidates have not been previously implicated for MetS risk. Mapped loci represent *MACF1* & *KIAA0754*, *GRB14* & *COBLL1* & *LOC646736-IRS1*, *SLC39A8*, *NELFE* & *SKIV2L* & *STK19*, *BAZ1B* & *BCL7B* & *TBL2* & *MLXIPL*, *HECTD4* & *PTPN11*, and *ZNF664*, where *MLXIPL* is already published for its association with MetS with a p-value < 0.01 [63]. They represent known loci identified as having multiple relationships at the level of single traits or T2D or CHD and not previously fully appreciated for their genetic pleiotropy. These findings summarized in Fig. 2, reinforce the importance of inflammatory responses as correlates of MetS and suggest that pleiotropic loci and their pathways contribute to the correlated architecture of MetS.

Kristiansson et al. [63] replicated 22 previously identified susceptibility loci for individual MetS risk factors, when testing for associations with MetS individual risk factors or with orthogonal factors from factor analysis. Most of the identified loci associated with lipid phenotypes and none were associated with two or more orthogonal MetS factors. Also they did not find evidence of pleiotropy of these genes with obesity. By comparison, our study based on very large GWAS meta-analyses indicates, that some MetS genes may be associated with two or more MetS risk factors, including inflammatory markers. For example, *MC4R* (rs6567160) showed associations with WAIST, BMI, HDLC, TG and CRP; *NELFE* (rs419788), *SKIV2L* (rs437179), *STK19* (rs389883) were associated with TG, WAIST, SBP, PAI-1, WBCC, and BMI; *SLC39A8* (rs13107325) was associated with HDLC, BMI, WAIST, SBP, DBP and ADIP; and *MACF1* (rs1537817) was associated with HDLC, CRP, TG, WAIST, and GLUC.

The bioinformatic research provided additional information not only in support of our findings, but also to a finer understanding of gene effects as is the case of *BAZ1B*, *PTPN11*, *TBL2*, *BCL7B* for heart valve disease, and *MLXIPL*, *LPL* and *GCKR* in relation to fatty liver disease as revealed by the Literature Lab. In contrast, our literature Entrez gene search based on trait keywords produced a filtered list of 48 pleiotropic candidate genes (Supplemental Table 6), from human, mouse and/or rat research. The 48 gene list can reflect also weakness. For example, if a gene association/effect is identified from a single study with a small sample size, the keyword search still considers it as a countable

contribution. Regardless of this weakness, keyword searches revealed that other genes with pleiotropic effects among metabolic traits themselves and also with inflammation remain to be discovered.

In principle, genetic makeup and environment contribute to the occurrence of MetS, whereas total burden is related to number and direction of disease predisposing alleles one carries. Our inferences are based on meta-analyses of p-values, and do not account for direction of associations for each SNP across studies (because some studies did not share beta-s and corresponding standard errors). This may represent a weaknesses in our study, for it could produce significance with heterogeneity. To diminish false positives we filtered our results for associations based on a meta $-\log_{10}p \geq 8$ and requiring individual associations of metabolic traits and inflammatory markers to have single trait-single SNP associations with $-\log_{10}p \geq 3$. We worked only with association GWAS meta-results mainly of large consortia, and because of not having access to raw data, it was not possible to evaluate mediation [132,133]. Because of large GWAS samples used, we expect follow up with functional tests can further elucidate the role of pleiotropy in MetS. In conclusion, several inflammatory markers are indeed part of metabolic syndrome. A pleiotropic genetic architecture exists and contributes to MetS. Among genes with pleiotropic associations in our study, specific alleles of the ones associating with ADIP and HDLC may further contribute in understanding how to protect from MetS.

Author contributions

A.T.K., J.B.M., I.B.B. conceived the study project; A.T.K., D.I.C., K.E.N., A.P.R., L.R.Y., T.O.K., J.A.S., A.D., J.D., M.G.L., B.Z.A., I.P., J.B.M., and I.B.B. researched data, contributed to discussion and wrote the manuscript; A.D.J., M.F.F., F.T.A., A.Y.C., I.M.N., Z.D., A.M., S.A.P., Y.V.S., M.D.R., A.V., H.L., S.L., L.M., R.R., Y.S., M.A.Z., H.K.I., R.B.S., T.J., M.E.J., T.H., O.P., R.P.S., H.S., A.H., A.G.U., O.H.F., M.A.I., J.B.R., C.R., J.G.W., L.L., S.K.G., M.N., L.J.R., J.S.P., J.C., W.T., W.H.L.K., E.B., A.C.M., P.M.R., D.M.B., J.I.R., S.L.R.K., R.J.F.L., Y.H., M.A.P., R.T., B.F.V., D.V., C.J.O., and E.J.B. researched data or contributed to discussion and reviewed/edited the manuscript.

Conflict of interest

All authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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