



Eating disinhibition and food liking are influenced by variants in CAV1 (caveolin 1) gene

This is the peer reviewed (post-print) version of the following article:

Original

Eating disinhibition and food liking are influenced by variants in CAV1 (caveolin 1) gene / Concas, M.p., Cocca, M., Catamo, E., Gasparini, P., Robino, A.. - In: FOOD QUALITY AND PREFERENCE. - ISSN 0950-3293. - 96:(2022), pp. 104447."-104447."-". [10.1016/j.foodqual.2021.104447]

Availability:

This version is available at: 11368/3025991 since: 2022-07-19T09:22:28Z

Publisher:

Published

DOI:10.1016/j.foodqual.2021.104447

Terms of use:

Some rights reserved. More details in the PostPrint rights section below.

License:

Attribution-NonCommercial-NoDerivatives 4.0 International

Publisher copyright

--

(Article begins on next page)

Eating disinhibition and food liking are influenced by variants in *CAV1* (caveolin 1) gene

Maria Pina Concas^{a,*}, Massimiliano Cocca^a, Eulalia Catamo^a, Paolo Gasparini^{a,b}, Antonietta Robino^a

^a Institute for Maternal and Child Health – IRCCS “Burlo Garofolo”, Via dell’Istria 65/1, 34137 Trieste, Italy

^b Department of Medical Sciences, University of Trieste, Strada di Fiume, 447, 34149 Trieste, Italy

ARTICLE INFO

Keywords:

Eating disinhibition
Food liking
Genome-wide association study
CAV1 gene
Metabolic measures

ABSTRACT

Eating behavior is influenced by a combination of environmental and genetic factors. Although candidate gene studies have been conducted, much remains to be understood about genetic influences. Therefore, we conducted a Genome-Wide Association Study (GWAS) aims to identify new variants that influence eating disinhibition. Moreover, we test the possible association of these variants with food liking and metabolic phenotypes.

We measured disinhibition in two cohorts of Italian samples using three selected statements from the Three-Factor Eating Questionnaire. Personal and clinical data were collected, as well as liking for different foods and beverages. GWAS was carried out in 1124 individuals; then the best signals (p -value $< 1 \times 10^{-5}$) were studied for replication in 426 independent participants. To study the link of eating disinhibition and associated variants with food liking and metabolic traits, we used linear mixed models and Structural Equation Modeling (SEM).

A significant association with *CAV1* (caveolin 1) gene ($p < 5 \times 10^{-8}$) was identified. The top SNP (rs6961694) resulted also associated with the liking for sweet foods and alcoholic beverages (p -value < 0.05). Moreover, we observed significant eQTL associations between this SNP and *CAV1* expression levels in human tissues such as adipose subcutaneous tissue, pancreas and brain hippocampus (p -value = 0.00022, 0.00015 and 0.017, respectively). Although higher values of BMI, waist, hips and triglycerides were significantly associated with increasing eating disinhibition (p -value < 0.05), no association emerged between the rs6961694 SNP and anthropometric or lipids phenotypes.

In conclusion, we describe a significant association between eating traits and *CAV1* gene, providing new knowledge on the link existing between genetics, eating behaviour and health status.

1. Introduction

Human eating behavior determines our food intake and preferences, influencing the development of diseases such as obesity, diabetes and cardiovascular diseases (Grimm and Steinle, 2011). Dietary restraint (the tendency to consciously restrict or control food intake) and disinhibition (the tendency to overeat in the presence of palatable foods or emotional stress) are eating-related constructs that assess behavioral control and attitudes toward food. In particular, eating disinhibition was associated with less healthful food choices such as higher liking or consumption of alcohol, high-fat and high-sugar foods and reduced consumption of vegetables, fruit and high-fiber bread (Contento et al., 2005; Lähteenmäki and Tuorila, 1995; Bryant, Finlayson, King, & Blundell, 2006; Bryant et al., 2007; Borg et al., 2004; Higgs and

Eskenazi, 2007). A relationship between disinhibition and high-energy intakes was also reported in obese individuals (Lindroos et al., 1997) while several studies have shown a link between this eating trait and Body Mass Index (BMI), weight gain over time and obesity development (Löffler et al., 2015; Bryant et al., 2007; Bellisle et al., 2004; Hays and Roberts, 2008; Williamson et al., 1995). Higher disinhibition was also associated with diabetes, increased insulin levels and glycemic control (Schwab et al., 2017; Straub et al., 1996) as well as hypertension or hyperlipidemia (Hainer et al., 2006).

Eating disinhibition is a complex trait influenced by genetic and environmental factors (Provencher et al., 2005; Rankinen and Bouchard, 2006).

The possible presence of genetic risk factors for individual eating disinhibition was already reported with heritability estimated ranging

* Corresponding author.

E-mail address: mariapina.concas@burlo.trieste.it (M.P. Concas).

between 0.19 and 0.45 (Steinle et al., 2002; Provencher et al., 2005; Neale et al., 2003). Linkage studies have first identified two loci on chromosomes 7 and 16 (Steinle et al., 2002) and, then, another locus on chromosome 15 spanning the *neuromedin β* gene (*NMB*). *NMB* is widely expressed in brain, pancreas, adrenal glands, and gastrointestinal tract. It is known to inhibit food intake in rat and it is involved in the modulation of the serotonergic (5-HT) system and the stimulation of pancreatic hormones (Kim and Mizuno, 2010; Yamano et al., 2002). A missense mutation in this gene resulted associated with disinhibition and susceptibility to hunger as well as to changes in body fat composition (Bouchard et al., 2004).

Candidate gene studies have also been carried out further supporting the role of genetic factors in eating behavior. For example, genes associated with taste perception, have been studied in relation to eating disinhibition identifying an association with *TAS2R38* bitter taste gene in Old Order Amish (Dotson et al., 2010). Choquette and colleagues also investigated the role of selected Olfactory Receptor (OR) genes in eating behavior founding an association between eating disinhibition and a SNP (rs2240927) in *OR7E24* (Choquette et al., 2012). Furthermore, genes previously associated with BMI or obesity have also been investigated, showing a role of *FTO* gene in loss of control overeating and selection of fat foods (Tanofsky-Kraff et al., 2009). Another related-obesity gene shown to be associated with disinhibition and hunger scores in obese individuals from a French cohort is *GAD2* (glutamate decarboxylase) (Boutin et al., 2003). Moreover, Meyre et al. (Meyre et al., 2005) reported an association between *GAD2* and lower birth weight and subsequently higher BMI Z-Scores in French children. Finally, *GAD2* gene was also associated with increased disinhibition, emotional susceptibility to disinhibition, susceptibility to hunger and weight gain over time in women from the Quebec Family Study (Choquette et al., 2009). A relationship between eating disinhibition and *AKR1B10* gene was also reported. *AKR1B10* encodes for an enzyme involved in detoxifying processes during digestion and its expression in brain regions potentially involved in eating behavior (such as nucleus accumbens and the frontal cortex) is diminished (Rohde et al., 2015).

Other studies on possible candidate genes (i.e., *5-HT2A*, *PPARG-gamma2*) linked to eating traits did not find association with disinhibition (Racine et al., 2009; Rosado et al., 2007).

Moreover, up to date, to our knowledge, no genome screening for associations between millions of genetic variants and eating disinhibition have been conducted. Therefore, in the present study, we investigated this line of research, reporting results of a GWAS for eating disinhibition carried out in an Italian cohort with replication in independent samples. Then, given the evidence in the literature of the influence of eating disinhibition on food choices and health, we verified the effect of this phenotype on food liking and metabolic parameters (e.g., BMI, waist-hip ratio (WHR), lipids). Finally, we used Structural Equation Modeling (SEM) and Sobel test to investigate the possible influence of the identified gene variants on food liking and metabolic parameters, clarifying the mediating effect of disinhibition.

2. Methods

This article used the STrengthening the REporting of Genetic Association Studies (STREGA) reporting guidelines (Little et al., 2009).

2.1. Study populations

The discovery phase of the study was carried out on 1124 individuals belonging to the Val Borbera (VB) cohort, in the North of Italy, while the replica phase was carried out in 426 individuals coming from Carlantino (CAR), a village in the South of Italy. Both populations belong to the Italian Network of Genetic Isolates (INGI), a project that aims to dissect the genetic basis of many diseases and phenotypes (including eating habits) taking advantage of these populations' genetic and environmental homogeneity. The Val Borbera is a large valley isolated from the

surrounding areas by mountains and characterized by high endogamy. Carlantino is a small village in southern Italy that was settled by a few founders at the end of the sixteenth century. A detailed description of these populations and their characteristics in term of relatedness structure have been previously reported (Xue et al., 2017; Cocca et al., 2020; Traglia et al., 2009). The ethical committees of San Raffaele Hospital and IRCCS Burlo Garofolo approved the study, and all participants signed the written informed consent.

Sample collection was conducted between 2004 and 2015. Participants aged ≥ 18 years and with completed data for eating disinhibition and genotyping have been included in the study.

2.2. Eating disinhibition

Eating disinhibition was evaluated based on the statements from the disinhibition subscale of the Three-Factor Eating Questionnaire (Stunkard and Messick, 1985), as previously described in Tepper et al. (Tepper et al., 2008). Briefly, disinhibition was assessed through three items: "Sometimes things just taste so good that I keep on eating even when I am no longer hungry", "I usually eat too much at social occasions, like parties and picnics" and "When I feel blue, I often overeat". An affirmative marking for each statement was scored 1 point (overall range from 0 to 3). The trait was used in statistical analysis as quantitative trait.

2.3. Food liking groups

Liking of different foods and beverages was assessed through a questionnaire. Each participant answered to the question "How much do you like it" for each food/beverage, rating the liking on a 9-point scale ranging from "dislike extremely" (score 1) to "like extremely" (score 9) (Pirastu et al., 2016; Tepper et al., 2008). The foods and beverages included in the questionnaire ranged from 58 in CAR and 63 or 106 in VB, in which two different surveys have been conducted, as better explained in our previous work (Concas et al., 2019). In [Online Resource Table 1](#) is reported the full list of items. We performed hierarchical clustering using Ward's D method, as implemented in the *hclust* function of R (www.r-project.org). We then defined a set of groups that showed a high level of within-group correlation across the individual food-liking items ([Online Resource Table 2](#)). Each "food liking group" was defined as the mean liking given by each individual to the foods belonging to a particular group. Finally, we evaluated the reliability of each group using the Cronbach alpha function available in R library *psy*.

2.4. Metabolic traits

BMI was obtained by the Bioelectrical Impedance Analysis technique using the Body Composition Analyzer (Tanita BC-420MA; Tanita, Tokyo, Japan). Waist and hip circumference (both in cm) were measured and WHR was calculated. Fasting venous blood was collected and used to perform routine biochemical analyses through Cobas 6000 analyzer (Roche).

2.5. Genotyping and imputation

All samples have been genotyped with Illumina 370 k high-density SNP array. Genotype imputation was conducted after standard quality control (sample call rate 0.95, SNP call rate 0.99, Hardy Weinberg Equilibrium test p-value 0.00001, Minimum Allele Frequency (MAF) 0.01) using IMPUTE2 (Howie et al., 2009) considering as reference a custom panel generated merging the 1000 Genomes phase 3 ([The 1000 Genomes Project Consortium, 2012](#)) and whole genome sequences of samples. After imputation, SNPs with MAF < 0.01 and Info Score < 0.4 were discarded from the statistical analyses. Detailed information are reported in our previous work (Cocca et al., 2020).

GWAS and replication analysis for eating disinhibition were conducted using mixed linear models as implemented in *ABEL* R packages (Aulchenko et al., 2007). Prior to genetic analysis, residuals of the trait were calculated by linear regression, using age and sex as covariates. The residuals were rank transformed to normal distribution (*rntransform* function in *GenABEL* R package (Aulchenko et al., 2007)) to be used in GWAS and replication analyses. Genomic kinship matrices were used as random effects to take into account relatedness. A two-step approach was implemented (Hirschhorn and Daly, 2005; Soranzo et al., 2009). First, a genome-wide discovery was carried out in 1124 individuals of the VB cohort. The SNPs showing association with the trait at the significance level of $p\text{-value} < 1 \times 10^{-5}$ were selected to be replicated in 426 individuals of the CAR cohort. In addition, we selected and tested 10 candidate SNPs (rs1726866, rs9939609, rs992990, rs7908975, rs2236418, rs10232478, rs782881, rs1834150, rs1051168, rs2240927) previously reported to be associated with eating disinhibition (Bouchard et al., 2004; Dotson et al., 2010; Tanofsky-Kraff et al., 2009; Boutin et al., 2003; Choquette et al., 2009; Rohde et al., 2015; Choquette et al., 2012).

Results were combined using an inverse-variance method (METAL) (Willer et al., 2010) to assess the effect and the significance of the selected SNPs in the combined samples. SNPs with $p\text{-value} < 5 \times 10^{-8}$ (the standard Bonferroni-corrected significance threshold for a GWAS) were considered as significant. While for the 10 candidate SNPs we applied a Bonferroni-adjusted significance threshold of $p < 0.005$ ($=0.05/10$ SNPs selected).

Linkage disequilibrium (LD) between SNPs was assessed in 548 whole genome sequences (424 from VB and 124 from CAR) using R library Genetics.

2.7. GTEx (Genotype-Tissue Expression) analysis

Analysis of gene expression levels was conducted in 14 human tissues using the GTEx (Genotype-Tissue Expression) Database, release v8 (The GTEx Consortium et al., 2015). GTEx eQTL browser is a central resource that records and shows the results of a research project for determining the association between genetic variation and high-throughput molecular-level expression phenotypes, and this information can help to better understand the biological relevance of results from GWA studies.

2.8. Relationship between eating disinhibition/SNPs and food liking groups and metabolic traits

To evaluate the relationship of eating disinhibition with food liking groups and metabolic parameters, linear mixed models were used. The same procedure was used to assess the relationship of the associated polymorphisms with food liking groups and metabolic parameters. Specifically, food liking groups and metabolic traits were considered as dependent variables and disinhibition or genetic polymorphisms as explanatory variables. Age and sex were added as covariates in all models. Because of the relatedness structures of VB and CAR samples, genomic pairwise kinship coefficients matrices were included in the models as a random effect, as implemented in *coxme* R package. The analyses were performed in each population separately and then the results were meta-analyzed (*rmeta* R package). Statistical significance was set at $p\text{-value} < 0.05$.

To better understand the complex interplay between the several variables, models were developed and tested with Structural Equation Modeling (SEM, *lavaan* R package) (SS Wright, 1921; Rosseel, 2012), a statistical technique allowing the identification of direct and indirect influences of variables. SEM is used when the response variable in one regression equation becomes a predictor in another. Sex, age and population (CAR or VB) were included in the models as potential confounders. Criteria for overall fit were chosen a priori: chi-square $p\text{-value}$

non-significant ($\chi^2 p > 0.05$), Confirmatory Fit Index (CFI) ≥ 0.92 , Tucker-Lewis Index (TLI) > 0.87 and Root Mean Square Error of Approximation (RMSEA) < 0.05 (Tabachnick, 2001). To assess the significance of the mediated model, Sobel test was used (Sobel, 1982).

All the analyses were performed using R (www.r-project.org) v.3.3.0.

3. Results

3.1. Sample features

1124 adults (age range 18–90 years) were included in the discovery phase while 426 (age range 18–89) in replication one. Table 1 shows the sample characteristics for both populations.

3.2. GWAS and replication study

Results of GWAS ($p\text{-value} < 1 \times 10^{-5}$) on eating disinhibition in discovery sample are reported in Online Resource Table 3. The effect of population stratification on the GWAS was negligible as confirmed by the value of the genomic inflation factor ($\lambda = 1.0004$). QQ-plot and Manhattan-plot are shown in Online Resource (Fig. 1 a-b). 195 SNPs reached a statistically suggestive threshold of $p\text{-value} < 1 \times 10^{-5}$ and were selected for replication. After replication, in the combined analysis, 18 SNPs reached a genome-wide significant threshold of 5×10^{-8} (Table 2). Results from the whole series of analysis are given in Online Resource Table 3. These SNPs are spanning a region of about 32 Kb in Caveolin 1 (*CAV1*) gene on chromosome 7. The regional plot is shown in Online Resource (Fig. 2). All SNPs are in linkage disequilibrium in both cohorts (i.e., minimum D' was 0.94 in VB and 0.98 in CAR). Because of this high LD, only one SNP (rs6961694, intronic, MAF 0.19) was selected for the following analysis.

Results show that the proportion of individuals carrying the major A allele at the homozygous state increases with the disinhibition level, as shown in Fig. 1. The variance of the trait explained by the SNP is 2.11% in the combined sample (2.45% in VB and 1.06% in CAR), calculated as difference of the coefficient of determination (R^2) in full model (age, sex and SNP) and base model (only age and sex).

No significant results were found for the 10 candidate SNPs previously associated with eating disinhibition (Online Resource Table 4).

3.3. rs6961694 and *CAV1* gene expression levels

Using GTEx, the association between rs6961694 and *CAV1* gene expression levels was analysed in multiple human tissues. Online Resource Table 5 report results for all the analysed tissues. The most

Table 1
Characteristics of individuals included in the study.

	Discovery sample VB	Replication sample CAR
N (%) women)	1124 (60.7%)	426 (54.2%)
Age, mean (standard deviation)	56.1 (16.5)	51.8 (17.1)
Disinhibition	2 [1–2]	1 [1–2]
Liking of Sweet foods	6.6 [5.4–7.4]	6.6 [5.2–7.7]
Liking of Alcoholic beverages	4.5 [3.2–6.0]	5.6 [3.8–7.0]
Liking of high-fat foods	6.8 [5.8–7.5]	7.2 [6.2–8.0]
BMI (Kg/m ²), mean (sd) (n)	25.6 (4.4) (1118)	26.4 (4.8) (365)
Hip (cm), mean (sd) (n)	89.9 (12.3) (1105)	88.02 (13.87) (310)
Waist (cm), mean (sd) (n)	98.72 (9.75) (405)	100.97 (11.44) (310)
WHR, mean (sd) (n)	0.90 (0.07) (405)	0.87 (0.08) (310)
Glucose, mg/dL, mean (sd) (n)	88.92 (14.79) (1106)	94.9 (16.94) (316)
Triglycerides, mg/dL, mean (sd) (n)	109.6 (59.7) (1112)	121.1 (59.9) (312)
Total Cholesterol, mg/dL, mean (sd) (n)	210.0 (39.2) (1118)	200.6 (46.9) (317)

When not specified, the values are median and interquartile interval.

Table 2

SNPs that reached genome-wide significance for association with eating disinhibition.

SNP	Chr	Position	Gene	Genomic location	Alleles ¹	Discovery sample VB (n = 1124)				Replication sample CAR (n = 426)				Combined sample (n = 1550)		
						freq A1 ²	Beta	se	p-value	freq A1 ²	Beta	se	p-value	Beta	se	p-value
rs6466582	7	116523049	CAV1	upstream_gene_variant	A/G	0.838	0.297	0.060	6.128E-07	0.800	0.232	0.089	8.767E-03	0.2769	0.0495	2.229E-08
rs6950593	7	116523256	CAV1	upstream_gene_variant	T/C	0.839	0.300	0.060	4.922E-07	0.810	0.219	0.090	1.459E-02	0.2751	0.0497	3.160E-08
rs7789052	7	116531457	CAV1	intron_variant	T/A	0.822	0.290	0.057	3.125E-07	0.814	0.206	0.090	2.223E-02	0.2663	0.0481	3.038E-08
rs6466583	7	116533010	CAV1	intron_variant	A/G	0.820	0.286	0.057	4.432E-07	0.812	0.204	0.090	2.285E-02	0.263	0.048	4.315E-08
rs7791631	7	116533547	CAV1	intron_variant	G/T	0.822	0.290	0.057	3.138E-07	0.814	0.206	0.090	2.222E-02	0.2662	0.0481	3.046E-08
rs4727834	7	116533914	CAV1	intron_variant	C/T	0.822	0.290	0.057	3.134E-07	0.814	0.206	0.090	2.221E-02	0.2662	0.0481	3.042E-08
rs4730749	7	116533991	CAV1	intron_variant	T/C	0.821	0.287	0.057	4.194E-07	0.812	0.205	0.090	2.278E-02	0.2634	0.048	4.085E-08
rs6943876	7	116534535	CAV1	intron_variant	A/G	0.821	0.287	0.057	4.182E-07	0.812	0.205	0.090	2.278E-02	0.2634	0.048	4.074E-08
rs1474510	7	116537403	CAV1	intron_variant	G/A	0.821	0.287	0.057	4.521E-07	0.813	0.206	0.090	2.222E-02	0.2636	0.0481	4.260E-08
rs3807986	7	116537771	CAV1	intron_variant	A/G	0.775	0.272	0.051	1.039E-07	0.788	0.179	0.086	3.661E-02	0.248	0.044	1.781E-08
rs1543293	7	116538494	CAV1	intron_variant	G/C	0.821	0.287	0.057	4.110E-07	0.812	0.205	0.090	2.278E-02	0.2635	0.048	4.007E-08
rs6466584	7	116539902	CAV1	intron_variant	C/G	0.822	0.290	0.057	3.099E-07	0.816	0.204	0.090	2.323E-02	0.2659	0.0481	3.159E-08
rs6466585	7	116539930	CAV1	intron_variant	C/G	0.822	0.290	0.057	3.096E-07	0.816	0.204	0.090	2.323E-02	0.2659	0.0481	3.156E-08
rs6466586	7	116540742	CAV1	intron_variant	T/C	0.822	0.290	0.057	3.095E-07	0.816	0.204	0.090	2.324E-02	0.2659	0.0481	3.156E-08
rs1476833	7	116541421	CAV1	intron_variant	G/T	0.822	0.290	0.057	3.092E-07	0.816	0.204	0.090	2.324E-02	0.2659	0.0481	3.153E-08
rs976739	7	116544477	CAV1	intron_variant	C/A	0.814	0.299	0.056	7.665E-08	0.820	0.195	0.091	3.272E-02	0.2711	0.0476	1.250E-08
rs3779514	7	116549129	CAV1	intron_variant	C/T	0.814	0.299	0.056	8.784E-08	0.821	0.196	0.091	3.201E-02	0.271	0.0477	1.381E-08
rs6961694	7	116555402	CAV1	intron_variant	A/G	0.814	0.299	0.056	7.664E-08	0.820	0.195	0.091	3.276E-02	0.2711	0.0476	1.249E-08

SNP	Chr	Position	Gene	Genomic location	Alleles ¹	Discovery sample VB (n=1124)				Replication sample CAR (n=426)				Combined sample (n=1550)		
						freq A1 ²	Beta	se	p-value	freq A1 ²	Beta	se	p-value	Beta	se	p-value
rs6466582	7	116523049	CAV1	upstream_gene_variant	A/G	0.838	0.297	0.060	6.128E-07	0.800	0.232	0.089	8.767E-03	0.2769	0.0495	2.229E-08
rs6950593	7	116523256	CAV1	upstream_gene_variant	T/C	0.839	0.300	0.060	4.922E-07	0.810	0.219	0.090	1.459E-02	0.2751	0.0497	3.160E-08
rs7789052	7	116531457	CAV1	intron_variant	T/A	0.822	0.290	0.057	3.125E-07	0.814	0.206	0.090	2.223E-02	0.2663	0.0481	3.038E-08
rs6466583	7	116533010	CAV1	intron_variant	A/G	0.820	0.286	0.057	4.432E-07	0.812	0.204	0.090	2.285E-02	0.263	0.048	4.315E-08
rs7791631	7	116533547	CAV1	intron_variant	G/T	0.822	0.290	0.057	3.138E-07	0.814	0.206	0.090	2.222E-02	0.2662	0.0481	3.046E-08
rs4727834	7	116533914	CAV1	intron_variant	C/T	0.822	0.290	0.057	3.134E-07	0.814	0.206	0.090	2.221E-02	0.2662	0.0481	3.042E-08
rs4730749	7	116533991	CAV1	intron_variant	T/C	0.821	0.287	0.057	4.194E-07	0.812	0.205	0.090	2.278E-02	0.2634	0.048	4.085E-08
rs6943876	7	116534535	CAV1	intron_variant	A/G	0.821	0.287	0.057	4.182E-07	0.812	0.205	0.090	2.278E-02	0.2634	0.048	4.074E-08
rs1474510	7	116537403	CAV1	intron_variant	G/A	0.821	0.287	0.057	4.521E-07	0.813	0.206	0.090	2.222E-02	0.2636	0.0481	4.260E-08
rs3807986	7	116537771	CAV1	intron_variant	A/G	0.775	0.272	0.051	1.039E-07	0.788	0.179	0.086	3.661E-02	0.248	0.044	1.781E-08
rs1543293	7	116538494	CAV1	intron_variant	G/C	0.821	0.287	0.057	4.110E-07	0.812	0.205	0.090	2.278E-02	0.2635	0.048	4.007E-08
rs6466584	7	116539902	CAV1	intron_variant	C/G	0.822	0.290	0.057	3.099E-07	0.816	0.204	0.090	2.323E-02	0.2659	0.0481	3.159E-08
rs6466585	7	116539930	CAV1	intron_variant	C/G	0.822	0.290	0.057	3.096E-07	0.816	0.204	0.090	2.323E-02	0.2659	0.0481	3.156E-08
rs6466586	7	116540742	CAV1	intron_variant	T/C	0.822	0.290	0.057	3.095E-07	0.816	0.204	0.090	2.324E-02	0.2659	0.0481	3.156E-08
rs1476833	7	116541421	CAV1	intron_variant	G/T	0.822	0.290	0.057	3.092E-07	0.816	0.204	0.090	2.324E-02	0.2659	0.0481	3.153E-08
rs976739	7	116544477	CAV1	intron_variant	C/A	0.814	0.299	0.056	7.665E-08	0.820	0.195	0.091	3.272E-02	0.2711	0.0476	1.250E-08
rs3779514	7	116549129	CAV1	intron_variant	C/T	0.814	0.299	0.056	8.784E-08	0.821	0.196	0.091	3.201E-02	0.271	0.0477	1.381E-08
rs6961694	7	116555402	CAV1	intron_variant	A/G	0.814	0.299	0.056	7.664E-08	0.820	0.195	0.091	3.276E-02	0.2711	0.0476	1.249E-08

All SNPs showed info score > 0.9 in discovery and replication sample.

¹Effect allele/Other allele; ² frequency of effect allele; beta = effect; se = standard error.

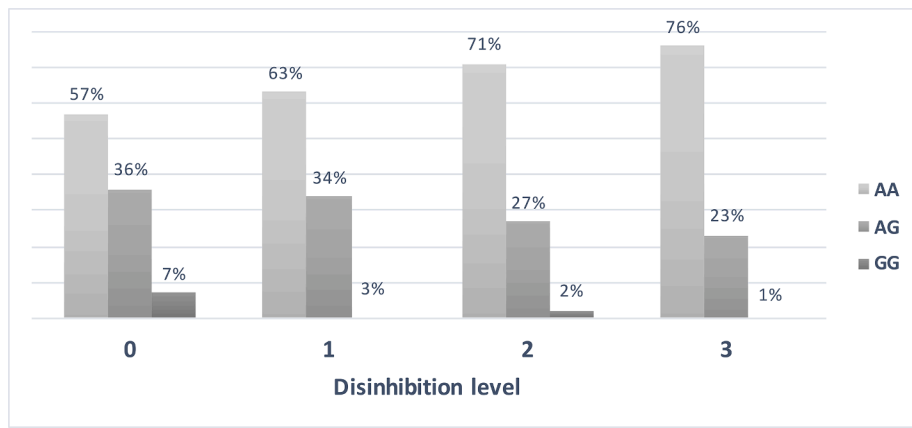


Fig. 1. Distribution of eating disinhibition levels by rs6961694 genotypes. 0, 1, 2, 3 refers to the level of disinhibition.

significant eQTL association was observed in adipose subcutaneous, pancreas and brain hippocampus tissues (p-value = 0.00022 and effect size = -0.11; p-value = 0.00015 and effect size = -0.39; p-value = 0.017 and effect size = -0.22, respectively). Overall, GTEX results revealed that the A allele was correlated with a reduced expression of *CAVI* gene.

3.4. Effect of disinhibition and rs6961694 on food liking

We checked the association of eating disinhibition and the SNP with three food liking groups: 1) alcoholic beverages (mean of the liking for alcohol, grappa, beer, dark beer, red wine, white wine, Cinzano, cherry), 2) sweet (mean of the liking for ice cream, panettone, whipped cream, milk chocolate, marzipan, biscuit, cake, icing, hazelnut cocoa spread, chocolate with cream) and 3) high-fat foods (mean of the liking for gorgonzola, goat cheese, pork chops, capicola, bacon, mortadella). All groups present Cronbach alpha higher than 0.6 as shown in [Online Resource Table 6](#).

For each food liking groups, a linear mixed model with sex, age and disinhibition as independent variables, and the genomic kinship as random effect was performed. Associations with disinhibition were found for all food liking groups (p-values < 0.05) as displayed in [Table 3](#). In particular, an increasing disinhibition corresponded to higher liking for all groups. In a second step, we verified if the SNP rs6961694 resulted also associated with liking groups, performing, for each group, a linear mixed model with sex, age and SNP as independent variables and the genomic kinship as random effect. We found association with alcohol beverages and sweet liking groups, but not with high-fat foods ([Table 3](#)). The direction of the association was the same as for eating disinhibition: AA individuals showed higher disinhibition and higher liking as compared to AG or GG ones.

Considering that both the SNP and the disinhibition level are associated with alcoholic beverages and sweet liking, SEM models were performed to test the direct and indirect effects of the SNP. The effect of rs6961694 on sweet food liking is not direct ([Fig. 2A](#)) but mediated by

Table 3

Results of association of food liking (response variable) with eating disinhibition and *CAVI* rs6961694 (independent variables).

Liking group	Disinhibition		rs6961694	
	Effect (95% CI)	p-value	Effect (95% CI)	p-value
Alcoholic beverages	0.127 (0.032, 0.223)	0.0088	0.265 (0.44, 0.092)	0.00258
Sweet foods	0.317 (0.237, 0.397)	<0.0001	0.154 (0.302, 0.006)	0.041
High-fat foods	0.149 (0.08, 0.217)	<0.0001	0.056 (-0.068, 0.18)	0.37

Models are sex and age adjusted.

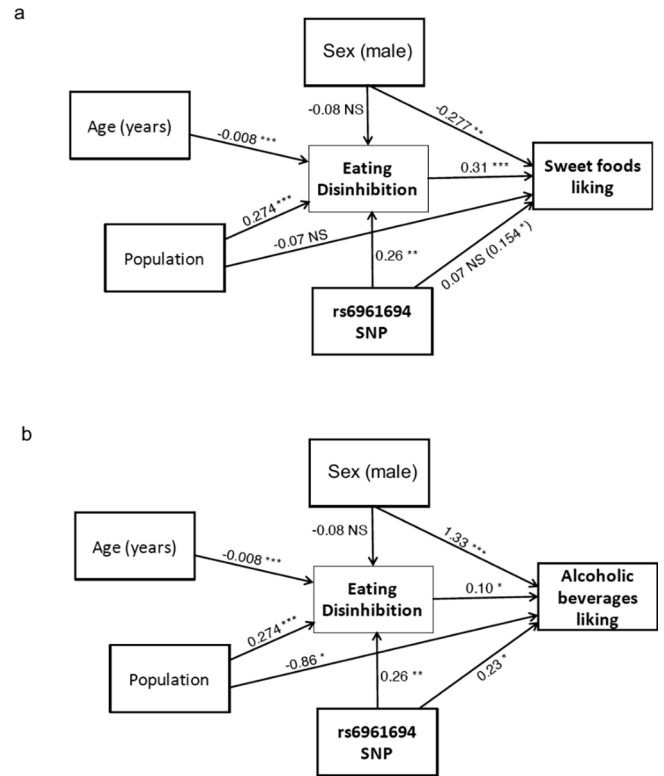


Fig. 2. Results of SEM models (Lavaan R package) for sweet liking (a) and alcoholic beverages (b) liking groups. Reported values are betas and p-values * ≤ 0.05 , ** ≤ 0.01 , *** ≤ 0.0001 . Pop = population (CAR/VB). In brackets are the values before eating disinhibition was added to the model. Both models had a good fit (CFI = 1.0, TLI = 1.04, p-value Chi-square = 0.63, RMSEA = 0.0 for sweet foods; CFI = 0.999, TLI = 0.994, p-value Chi-square = 0.269, RMSEA = 0.012 for alcoholic beverages). The relationship of the SNP with sweet liking was completely mediated by eating disinhibition (Sobel test, $z = -4.57$, p-value < 0.001) while the relationship with alcoholic beverages was direct and not mediated by disinhibition (Sobel test, $z = -0.31$, p-value = 0.76).

disinhibition (Sobel test, $z = -4.57$, p-value < 0.001), while the effect on alcoholic beverages is direct ([Fig. 2B](#)) and not mediated by disinhibition (Sobel test, $z = -0.31$, p-value = 0.76). Both SEM models had good fit parameters (CFI = 1.0, TLI = 1.04, p-value Chi-square = 0.63, RMSEA = 0.0 for sweet foods; CFI = 0.999, TLI = 0.994, p-value Chi-square = 0.269, RMSEA = 0.012 for alcoholic beverages).

Table 4 describes the results of the association of metabolic measures with disinhibition or rs6961694 SNP. Linear mixed model, with sex and age used as independent variables and the genomic kinship as random effect, showed significant association between increasing eating disinhibition and higher levels of BMI, waist, hips and triglycerides. While no association was found between rs6961694 and all metabolic traits investigated.

4. Discussion

In the present study, we identified a novel association between single nucleotide polymorphisms in the *CAVI* gene and eating disinhibition. For the top SNP, rs6961694, we observed that the more frequent allele A is associated with higher levels of disinhibition, and the SNP explained the 2.11% of the variance of the trait. Considering that eating disinhibition is a complex trait, determined by several genetic and environmental factors, this portion of explained variance is in line with other studies on multifactorial traits (Zhong et al., 2019).

rs6961694 was found to be also associated with liking of alcoholic beverages and of sweet foods. In particular, AA homozygous participants showed either higher disinhibition level and higher sweet and alcohol liking than GG and AG ones. A significant eQTL association was observed in adipose tissues, pancreas and brain hippocampus, being the A allele associated with a reduced expression of the *CAVI* gene. GTEx data further support previous findings demonstrating a positive correlation between decreased expression of *CAVI* gene and reduced lipogenic gene expression in the visceral adipose tissue of obese individuals (Fernández-Real et al., 2010).

Interestingly, *CAVI* is involved in lipid metabolism, and variants in this gene have already been associated with diabetes, metabolic syndrome, hypertension, triglycerides and coronary heart disease (Grilo et al., 2006; Yamada et al., 2007; Pojoga et al., 2011; Mora-García et al., 2018; Baudrand et al., 2015; Chen et al., 2016). The role of *CAVI* in glucose and lipid metabolism has also been elucidated through several studies in animal models. For example, *CAVI* knockout mice have been reported to have adipocyte abnormalities and increased levels of triglycerides and free fatty acids (Razani et al., 2002; Park et al., 2002). Moreover, an influence of *CAVI* on blood glucose regulation by interacting with the insulin receptor or with the GLUT4-mediated glucose transport has been shown (González-Muñoz et al., 2009).

Although no influence of rs6961694 *CAVI* SNP in eating traits is previously described, very recent evidence has reported for an association of another *CAVI* variant (rs3807992) and dietary fat intake (Abaj and Mirzaei, 2021; Khatibi et al., 2021). Authors also described a gene-diet interaction between rs3807992 SNP and healthy diet in relation to cardio-metabolic risk factors and metabolic disease. Moreover, Shyu et al. have reported that the effect of *CAVI* SNPs on ischemic stroke risk is significantly influenced by alcohol drinking (Shyu et al., 2017).

Our findings highlight that eating disinhibition and genetic variants may cooperate in defining individual food liking. Using SEM models and the Sobel test, we assessed the direct and indirect effects of eating disinhibition and associated variant on food liking. Results showed that the effect of *CAVI* SNP on sweet food liking was mediated by disinhibition, while the effect on alcoholic beverages was direct.

SEM and the Sobel test allowed us to understand the complex genetics-eating traits association better, clarifying the disinhibition's mediating effects. Moreover, our data confirm that high eating disinhibition is associated with higher BMI, waist, hips and triglycerides (Löffler et al., 2015; Bryant et al., 2007; Bellisle et al., 2004; Hays and Roberts, 2008; Williamson et al., 1995). On the contrary, no significant association has emerged connecting the rs6961694 *CAVI* variant and metabolic measures in our work. Although a relationship between another variant (rs11773845, no in LD with our SNP) in *CAVI* and triglycerides is previously reported (Grilo et al., 2006), our result supports

Table 4

Results of association of metabolic measures (response variable) with eating disinhibition and rs6961694 as independent variables (sex and age adjusted).

Metabolic traits	Disinhibition		rs6961694	
	Effect (95% CI)	p-value	Effect (95% CI)	p-value
BMI, Kg/m ²	0.751 (0.537,0.966)	<0.0001	-0.202 (-0.619,0.215)	0.34
WHR	0.003 (-0.002,0.007)	0.23	-0.001 (-0.009,0.007)	0.81
Waist, cm	1.794 (1.230,2.358)	<0.0001	-0.655 (-1.732,0.423)	0.23
Hips, cm	1.82 (1.098,2.542)	<0.0001	-0.775 (-2.141,0.59)	0.27
Glucose, mg/dL	0.701 (-0.066,1.467)	0.07	0.346 (-1.083,1.776)	0.64
Triglycerides, mg/dL	3.308 (0.231,6.385)	0.035	1.772 (-4.032,7.575)	0.55
Total Cholesterol, mg/dL	-0.323 (-2.39,1.744)	0.76	-1.316 (-5.248,2.626)	0.51

other published findings showing no association between *CAVI* gene and the metabolic measures (Mora-García et al., 2018; Baudrand et al., 2015). Larger sample size may probably be needed to detect associations between the *CAVI* SNP and metabolic traits.

In fact, compared to most GWASs that include thousands of individuals, our study consists of a limited number of participants. However, despite the small sample size, combining discovery and replication samples, we could detect a genome-wide significant association. The small sample size could also be on the basis of the lack of replica of variants in genes previously found associated with disinhibition in other studies. Moreover, the different way used to measure the disinhibition may also contribute to this lack of association. However, the true-false items of the three-factor eating questionnaire we used allowed a rapid collection of disinhibition measure as well as the identification of significant relationship with BMI and metabolic traits.

The present study includes correlation analysis, thus does not imply causality. Another limitation of our study is that *in silico* analysis to determine the relationship between *CAVI* expression and the variant of interest could not be confirmed in our participants because measures of *CAVI* expression are not available. Finally, the mechanism that underlies the association between the *CAVI* variant and eating traits is still to be elucidated and we do not have actual intake data to verify the possible effect of *CAVI* on food consumption.

5. Conclusion

Our study reports evidence for an association of *CAVI* with eating traits, suggesting that *CAVI* may be a possible candidate gene for eating disinhibition and specific food liking. Additional studies are needed to confirm present findings and to better understand the complex relationship existing between genetics, eating traits and food liking.

This information may help to early identify individuals susceptible for altered eating behaviours and then could be used to develop targeted interventions or define specific recommendations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all the participants to the project.

A sincere thank you to Veronika Collovati for her proofreading of this manuscript.

MPC, PG, AR designed research; MPC, AR, EC conducted research; MC, PG provided essential reagents and materials (including databases); MPC, AR analyzed data or performed statistical analysis; MPC, AR wrote paper. All authors read and approved the final manuscript.

Funding

This work was supported by Italian Ministry of Health (RC 35/2017) and IRCCS Burlo Garofolo of Trieste (5X1000 funding).

Ethics approval

The study was approved by the ethical committees of San Raffaele Hospital and IRCCS Burlo Garofolo. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

This manuscript is not being simultaneously submitted or published elsewhere.

Availability of data and material

Data described in the manuscript will be made available upon request.

A subset of the data is already available on the European Genome-phenome Archive (EGA) at the following links:

VB cohort: BAM files https://www.ebi.ac.uk/ega/studies/EGA_S00001000398; <https://www.ebi.ac.uk/ega/studies/EGAS00001000458>;

CAR cohort: BAM files <https://www.ebi.ac.uk/ega/studies/EGAS00001000460>;

A vcf file including all the variants (SNPs and INDELs) with information on allele frequencies in the whole dataset and each cohort, has been submitted to the European Variation Archive (EVA), study accession number: PRJEB33648. The data are accessible at the following link: <https://www.ebi.ac.uk/ena/data/view/PRJEB33648>.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.foodqual.2021.104447>.

References

Abaj, F., & Mirzaei, K. (2021). Caveolin-1 genetic polymorphism interacts with PUFA to modulate metabolic syndrome risk. *British Journal of Nutrition*, 1–8. <https://doi.org/10.1017/S0007114521002221>

Aulchenko, Y. S., Ripke, S., Isaacs, A., & van Duijn, C. M. (2007). GenABEL: An R library for genome-wide association analysis. *Bioinformatics*, 23(10), 1294–1296. <https://doi.org/10.1093/bioinformatics/btm108>

Baudrand, R., Goodarzi, M. O., Vaidya, A., Underwood, P. C., Williams, J. S., Jeunemaitre, X., ... Pojoga, L. H. (2015). A prevalent caveolin-1 gene variant is associated with the metabolic syndrome in Caucasians and Hispanics. *Metabolism*, 64(12), 1674–1681. <https://doi.org/10.1016/j.metabol.2015.09.005>

Bellisle, F., Clément, K., Le Barzic, M., Le Gall, A., Guy-Grand, B., & Basdevant, A. (2004). The Eating Inventory and Body Adiposity from Leanness to Massive Obesity: A Study of 2509 Adults. *Obesity Research*, 12, 2023–2030. <https://doi.org/10.1038/oby.2004.253>

Borg, P., Fogelholm, M., & Kukkonen-Harjula, K. (2004). Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men. *International Journal of Obesity*, 28(12), 1548–1554. <https://doi.org/10.1038/sj.ijo.0802790>

Bouchard, L., Drapeau, V., Provencher, V., Lemieux, S., Chagnon, Y., Rice, T., Rao, D., Vohl, M.-C., Tremblay, A., Bouchard, C., Périus, L., 2004. Neuromedin β : a strong candidate gene linking eating behaviors and susceptibility to obesity. *The American Journal of Clinical Nutrition* 80, 1478–1486. doi: 10.1093/ajcn/80.6.1478.

Boutin, P., Dina, C., Vasseur, F., Dubois, S., Corset, L., Séron, K., et al. (2003). GAD2 on Chromosome 10p12 Is a Candidate Gene for Human Obesity. *PLoS Biology*, 1(3), e68. <https://doi.org/10.1371/journal.pbio.0000068>

Bryant, E. J., Finlayson, G., King, N. A., & Blundell, J. E. (2006). The influence of acute exercise on liking and preference for food on high trait disinhibition women. *Obesity Reviews*.

Bryant, E. J., King, N. A., & Blundell, J. E. (2007). Disinhibition: Its effects on appetite and weight regulation: Disinhibition's effects on weight regulation. *Obesity Reviews*, 9, 409–419. <https://doi.org/10.1111/j.1467-789X.2007.00426.x>

Chen, S., Wang, X., Wang, J., Zhao, Y., Wang, D., Tan, C., et al. (2016). Genomic variant in CAV1 increases susceptibility to coronary artery disease and myocardial infarction. *Atherosclerosis*, 246, 148–156. <https://doi.org/10.1016/j.atherosclerosis.2016.01.008>

Choquette, A. C., Bouchard, L., Drapeau, V., Lemieux, S., Tremblay, A., Bouchard, C., et al. (2012). Association between olfactory receptor genes, eating behavior traits and adiposity: Results from the Quebec Family Study. *Physiology & Behavior*, 105(3), 772–776. <https://doi.org/10.1016/j.physbeh.2011.10.015>

Choquette, A. C., Lemieux, S., Tremblay, A., Drapeau, V., Bouchard, C., Vohl, M.-C., & Périus, L. (2009). GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study. *Physiology & Behavior*, 98(4), 505–510. <https://doi.org/10.1016/j.physbeh.2009.08.004>

Cocca, M., Barbieri, C., Concas, M. P., Robino, A., Brumat, M., Gandin, I., et al. (2020). A bird's-eye view of Italian genomic variation through whole-genome sequencing. *European Journal of Human Genetics*, 28(4), 435–444. <https://doi.org/10.1038/s41431-019-0551-x>

Concas, M. P., Catamo, E., Biino, G., Toniolo, D., Gasparini, P., & Robino, A. (2019). Factors associated with food liking and their relationship with metabolic traits in Italian cohorts. *Food Quality and Preference*, 75, 64–70. <https://doi.org/10.1016/j.foodqual.2019.02.010>

Contento, L., Zybert, P., & Williams, S. (2005). Relationship of cognitive restraint of eating and disinhibition to the quality of food choices of Latina women and their young children. *Preventive Medicine*, 40(3), 326–336. <https://doi.org/10.1016/j.ypmed.2004.06.008>

Dotson, C. D., Shaw, H. L., Mitchell, B. D., Munger, S. D., & Steinle, N. I. (2010). Variation in the gene TAS2R38 is associated with the eating behavior disinhibition in Old Order Amish women. *Appetite*, 54(1), 93–99. <https://doi.org/10.1016/j.appet.2009.09.011>

Fernández-Real, J. M., Catalán, V., Moreno-Navarrete, J. M., Gómez-Ambrosi, J., Ortega, F. J., Rodríguez-Hermosa, J. I., et al. (2010). Study of caveolin-1 gene expression in whole adipose tissue and its subfractions and during differentiation of human adipocytes. *Nutr Metab (Lond)*, 7(1), 20. <https://doi.org/10.1186/1743-7075-7-20>

González-Muñoz, E., López-Iglesias, C., Calvo, M., Palacín, M., Zorzano, A., & Camps, M. (2009). Caveolin-1 loss of function accelerates glucose transporter 4 and insulin receptor degradation in 3T3-L1 adipocytes. *Endocrinology*, 150, 3493–3502. <https://doi.org/10.1210/en.2008-1520>

Grilo, A., Fernandez, M., Beltrán, M., Ramirez-Lorca, R., González, M., Royo, J., et al. (2006). Genetic analysis of CAV1 gene in hypertension and metabolic syndrome. *Thrombosis and Haemostasis*, 95(04), 696–701.

Grimm, E. R., & Steinle, N. I. (2011). Genetics of eating behavior: Established and emerging concepts. *Nutrition Reviews*, 69, 52–60. <https://doi.org/10.1111/j.1753-4887.2010.00361.x>

Hainer, V., Kunesova, M., Bellisle, F., Parizkova, J., Braunerova, R., Wagenknecht, M., et al. (2006). The Eating Inventory, body adiposity and prevalence of diseases in a quota sample of Czech adults. *International Journal of Obesity*, 30(5), 830–836. <https://doi.org/10.1038/sj.ijo.0803202>

Hays, N. P., & Roberts, S. B. (2008). Aspects of eating behaviors “disinhibition” and “restraint” are related to weight gain and BMI in women. *Obesity*, 16, 52–58. <https://doi.org/10.1038/oby.2007.12>

Higgs, S., & Eskenazi, T. (2007). Dietary restraint and disinhibition are associated with increased alcohol use behaviours and thoughts in young women social drinkers. *Eating Behaviors*, 8(2), 236–243. <https://doi.org/10.1016/j.eatbeh.2006.06.007>

Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics*, 6(2), 95–108. <https://doi.org/10.1038/nrg1521>

Howie, B. N., Donnelly, P., Marchini, J., & Schork, N. J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genetics*, 5(6), e1000529. <https://doi.org/10.1371/journal.pgen.1000529>

Khatibi, N., Mirzababaei, A., Shiraseb, F., Abaj, F., Koohdani, F., & Mirzaei, K. (2021). Interactions between caveolin 1 polymorphism and the Mediterranean and Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND) diet on metabolic dyslipidemia in overweight and obese adult women: A cross-sectional study. *BMC Research Notes*, 14, 364. <https://doi.org/10.1186/s13104-021-05777-4>

Kim, E. R., & Mizuno, T. M. (2010). Role of neurotensin receptor 1 in the regulation of food intake by neuromedins and neuromedin-related peptides. *Neuroscience Letters*, 468(1), 64–67. <https://doi.org/10.1016/j.neulet.2009.10.064>

Lähteenmäki, L., & Tuorila, H. (1995). Three-factor eating questionnaire and the use and liking of sweet and fat among dieters. *Physiology & Behavior*, 57(1), 81–88. [https://doi.org/10.1016/0031-9384\(94\)00210-V](https://doi.org/10.1016/0031-9384(94)00210-V)

Lindroos, A.-K., Lissner, L., Mathiassen, M. E., Karlsson, J., Sullivan, M., Bengtsson, C., & Sjöström, L. (1997). Dietary Intake in Relation to Restrained Eating, Disinhibition, and Hunger in Obese and Nonobese Swedish Women. *Obesity Research*, 5, 175–182. <https://doi.org/10.1002/j.1550-8528.1997.tb00290.x>

Little, J., Higgins, J.P.T., Ioannidis, J.P.A., Moher, D., Gagnon, F., von Elm, E., et al., 2009. STrengthening the REporting of Genetic Association studies (STREGA) - an

- p>extension of the STROBE statement.
- European Journal of Clinical Investigation*
- 39, 247–266. doi: 10.1111/j.1365-2362.2009.02125.x.
- Löffler, A., Luck, T., Then, F. S., Sikorski, C., Kovacs, P., Böttcher, Y., et al. (2015). Eating behaviour in the general population: an analysis of the factor structure of the german version of the three-factor-eating-questionnaire (TFEQ) and its association with the body mass index. *PLoS ONE*, 10(7), e0133977. <https://doi.org/10.1371/journal.pone.0133977>
- Meyre, D., Boutin, P., Tounian, A., Deweirdt, M., Aout, M., Jouret, B., et al. (2005). Is glutamate decarboxylase 2 (GAD2) a genetic link between low birth weight and subsequent development of obesity in children? *The Journal of Clinical Endocrinology & Metabolism*, 90(4), 2384–2390. <https://doi.org/10.1210/jc.2004-1468>
- Mora-García, G., Gómez-Camargo, D., Alario, Á., & Gómez-Alegría, C. (2018). A common variation in the caveolin 1 gene is associated with high serum triglycerides and metabolic syndrome in an admixed latin american population. *Metabolic Syndrome and Related Disorders*, 16(9), 453–463. <https://doi.org/10.1089/met.2018.0004>
- Neale, B. M., Mazzeo, S. E., & Bulik, C. M. (2003). A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). *Twin Res*, 6, 471–478. <https://doi.org/10.1375/13690520322686455>
- Park, D. S., Woodman, S. E., Schubert, W., Cohen, A. W., Frank, P. G., Chandra, M., et al. (2002). Caveolin-1/3 double-knockout mice are viable, but lack both muscle and non-muscle caveolae, and develop a severe cardiomyopathic phenotype. *The American Journal of Pathology*, 160(6), 2207–2217. [https://doi.org/10.1016/S0002-9440\(10\)61168-6](https://doi.org/10.1016/S0002-9440(10)61168-6)
- Pirastu, N., Kooyman, M., Traglia, M., Robino, A., Willems, S. M., Pistis, G., et al. (2016). A genome-wide association study in isolated populations reveals new genes associated to common food likings. *Rev Endocr Metab Disord*, 17(2), 209–219. <https://doi.org/10.1007/s11154-016-9354-3>
- Pojoga, L. H., Underwood, P. C., Goodarzi, M. O., Williams, J. S., Adler, G. K., Jeunemaitre, X., et al. (2011). Variants of the caveolin-1 gene: A translational investigation linking insulin resistance and hypertension. *The Journal of Clinical Endocrinology & Metabolism*, 96(8), E1288–E1292. <https://doi.org/10.1210/jc.2010-2738>
- Provencher, V., Pérusse, L., Bouchard, L., Drapeau, V., Bouchard, C., Rice, T., Rao, D.C., Tremblay, A., Després, J.-P., Lemieux, S., 2005. Familial Resemblance in Eating Behaviors in Men and Women from the Quebec Family Study. *Obesity Research* 13, 1624–1629. doi: 10.1038/oby.2005.199.
- Racine, S. E., Culbert, K. M., Larson, C. L., & Klump, K. L. (2009). The possible influence of impulsivity and dietary restraint on associations between serotonin genes and binge eating. *Journal of Psychiatric Research*, 43(16), 1278–1286. <https://doi.org/10.1016/j.jpsychires.2009.05.002>
- Rankinen, T., & Bouchard, C. (2006). Genetics of Food Intake and Eating Behavior Phenotypes in Humans. *Annual Review of Nutrition*, 26(1), 413–434. <https://doi.org/10.1146/annurev.nutr.26.061505.111218>
- Razani, B., Combs, T. P., Wang, X. B., Frank, P. G., Park, D. S., Russell, R. G., et al. (2002). Caveolin-1-deficient mice are lean, resistant to diet-induced obesity, and show hypertriglyceridemia with adipocyte abnormalities. *Journal of Biological Chemistry*, 277(10), 8635–8647. <https://doi.org/10.1074/jbc.M110970200>
- Rohde, K., Federbusch, M., Horstmann, A., Keller, M., Villringer, A., Stumvoll, M., et al. (2015). Genetic variants in AKR1B10 associate with human eating behavior. *BMC Genetics*, 16(1). <https://doi.org/10.1186/s12863-015-0189-9>
- Rosado, E. L., Bressan, J., Martins, M. F., Cecon, P. R., & Martínez, J. A. (2007). Polymorphism in the PPARgamma2 and beta2-adrenergic genes and diet lipid effects on body composition, energy expenditure and eating behavior of obese women. *Appetite*, 49(3), 635–643. <https://doi.org/10.1016/j.appet.2007.04.003>
- Rosseel, Y. (2012). lavaan: an R package for structural equation modeling. *Journal of Statistical Software*, 48, 1–36. <https://doi.org/10.18637/jss.v048.i02>
- Schwab, S., Xu, T., Ryan, K., & Steinle, N. (2017). Eating behavior disinhibition predicts insulin resistance in the Old Order Amish. *J Hum Nutr Food Sci*, 5, 1109.
- Shyu, H.-Y., Chen, M.-H., Hsieh, Y.-H., Shieh, J.-C., Yen, L.-R., Wang, H.-W., et al. (2017). Association of eNOS and Cav-1 gene polymorphisms with susceptibility risk of large artery atherosclerotic stroke. *PLoS ONE*, 12(3), e0174110. <https://doi.org/10.1371/journal.pone.0174110>
- Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological Methodology*, 13, 290–312. <https://doi.org/10.2307/270723>
- Soranzo, N., Spector, T. D., Mangino, M., Kühnel, B., Rendon, A., Teumer, A., et al. (2009). A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium. *Nature Genetics*, 41(11), 1182–1190. <https://doi.org/10.1038/ng.467>
- Wright, S. S. (1921). Correlation and causation. *Journal of Agricultural Research*, 20, 557–585.
- Steinle, N.I., Hsueh, W.-C., Snitker, S., Pollin, T.I., Sakul, H., St Jean, P.L., Bell, C.J., Mitchell, B.D., Shuldiner, A.R., 2002. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. *The American Journal of Clinical Nutrition* 75, 1098–1106. doi: 10.1093/ajcn/75.6.1098.
- Straub, R.H., Lamparter-Lang, R., Palitzsch, K.D., Schölmerich, J., 1996. Association between eating behaviour and current glycaemic control, body mass or autonomic nervous function in long-term type I and type II diabetic patients. *Eur J Clin Invest* 26, 564–568. doi: 10.1046/j.1365-2362.1996.1720529.x.
- Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *Journal of Psychosomatic Research*, 29(1), 71–83. [https://doi.org/10.1016/0022-3999\(85\)90010-8](https://doi.org/10.1016/0022-3999(85)90010-8)
- Tabachnick, 2001. Using Multivariate Statistics. Boston, MA, USA.
- Tanofsky-Krass, M., Han, J.C., Anandalingam, K., Shomaker, L.B., Columbo, K.M., Wolkoff, L.E., et al., 2009. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. *The American Journal of Clinical Nutrition* 90, 1483–1488. <https://doi.org/10.3945/ajcn.2009.28439>.
- Tepper, B.J., Koelliker, Y., Zhao, L., Ullrich, N.V., Lanzara, C., D'Adamo, P., Ferrara, A., Ulivi, S., Esposito, L., Gasparini, P., 2008. Variation in the Bitter-taste Receptor Gene TAS2R38 , and Adiposity in a Genetically Isolated Population in Southern Italy. *Obesity* 16, 2289–2295. doi: 10.1038/oby.2008.357.
- The 1000 Genomes Project Consortium. (2012). An integrated map of genetic variation from 1,092 human genomes. *Nature*, 491, 56–65. <https://doi.org/10.1038/nature11632>
- The GTEx Consortium, Ardlie, K. G., Deluca, D. S., Segre, A. V., Sullivan, T. J., Young, T. R., et al. (2015). The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science*, 348(6235), 648–660. <https://doi.org/10.1126/science.1262110>
- Traglia, M., Sala, C., Masciullo, C., Cverhova, V., Lori, F., Pistis, G., et al. (2009). Heritability and demographic analyses in the large isolated population of val borbera suggest advantages in mapping complex traits genes. *PLoS ONE*, 4(10), e7554. <https://doi.org/10.1371/journal.pone.0007554>
- Willer, C. J., Li, Y., & Abecasis, G. R. (2010). METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, 26(17), 2190–2191. <https://doi.org/10.1093/bioinformatics/btq340>
- Williamson, D.A., Lawson, O.J., Brooks, E.R., Wozniak, P.J., Ryan, D.H., Bray, G.A., Duchmann, E.G., 1995. Association of body mass with dietary restraint and disinhibition. *Appetite* 25, 31–41. doi: 10.1006/appe.1995.0039.
- Xue, Y., Mezzavilla, M., Haber, M., McCarthy, S., Chen, Y., Narasimhan, V., et al. (2017). Enrichment of low-frequency functional variants revealed by whole-genome sequencing of multiple isolated European populations. *Nature Communications*, 8(1). <https://doi.org/10.1038/ncomms15927>
- Yamada, Y., Ando, F., & Shimokata, H. (2007). Association of gene polymorphisms with blood pressure and the prevalence of hypertension in community-dwelling Japanese individuals. *International Journal of Molecular Medicine*, 19, 675–683.
- Yamano, M., Ogura, H., Okuyama, S., & Ohki-Hamazaki, H. (2002). Modulation of 5-HT system in mice with a targeted disruption of neuromedin B receptor. *Journal of Neuroscience Research*, 68(1), 59–64. <https://doi.org/10.1002/jnr.v68:110.1002/jnr.10194>
- Zhong, V. W., Kuang, A., Danning, R. D., Kraft, P., van Dam, R. M., Chasman, D. I., & Cornelis, M. C. (2019). A genome-wide association study of bitter and sweet beverage consumption. *Human Molecular Genetics*, 28, 2449–2457. <https://doi.org/10.1093/hmg/ddz061>