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REVIEW

Interplay between diet and genetic susceptibility in obesity and related traits

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Abstract **The incidence of obesity has been rapidly increasing, and this condition has become a major public health threat. A substantial shift in environmental factors and lifestyle, such as unhealthy diet, is among the major driving forces of the global obesity pandemic. Longitudinal studies and randomized intervention trials have shown that genetic susceptibility to obesity may interact with dietary factors in relation to the body mass index and risk of obesity. This review summarized data from recent longitudinal studies and intervention studies on variations and diets and discussed the challenges and future prospects related to this area and public health implications.**

Keywords diet; genetic susceptibility; obesity; interaction

Introduction

Obesity and related metabolic diseases, such as type 2 diabetes and cardiovascular disease, have rapidly increased. The increasing epidemic of obesity is substantially attributed to environmental susceptibility to weight gain, such as unhealthy diets. As one of the main efforts against obesity and its complications, emerging dietary interventions have been conducted to improve weight loss and long-term weight maintenance [1,2]. Although several diets generally show no significant differences in their effectiveness on weight loss, considerable inter-individual heterogeneity has been identified in participants' response, and genetic background may partly account for such variability [3–5]. With revolutionary advancements in genomic technologies, a large body of genome-wide association studies (GWAS) have identified numerous obesity-associated genetic variants [6]. Growing data from longitudinal studies and randomized intervention trials have shown that genetic variations may interact with dietary factors in relation to obesity and related metabolic diseases.

Gene–environment rationale

Gene–environment interaction studies aim to examine how genetic and environmental factors jointly influence the trait of interest [7]. In this context, genes and environmental exposures may contribute to the developing risk of a condition in the same individual with genetic predisposition affecting the sensitivity to environmental exposures.

The genetic predisposition to obesity has its origins in our evolutionary history, although the obesity pandemic in the past was likely due to dramatic environmental changes. Several hypotheses have been proposed to explain the obesity pandemic in modern society and provided insights into gene–environment interaction within the understanding of human evolution. The "thrifty genotype" hypothesis explains that promoting efficient fat deposition was beneficial to survival during famine in early times, but it has become disadvantageous in modern societies because of the prepared fat deposition for famine that has yet to occur [8]. According to this hypothesis, individuals who carry "thrifty genes" are more susceptible to obesity under the same environmental exposure compared with those who do not carry these genes. An alternative perspective has been proposed, namely, "drifty gene" hypothesis, which elaborates that genes favoring obesity have not been positively selected but have rather been subjected to random drifting because of an absence of selection [9]. Nevertheless, further studies are needed to validate these

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theories and improve the understanding of gene–environment interactions.

Evidence from observational studies

A credible gene–environment interaction requires successful replications and biological plausibility [7], which increase the difficulty in detecting interactions. Nevertheless, several large-scale prospective studies with replication have sprung up in the burgeoning area of gene–environment interaction (Table 1).

An increase in the consumption of sugar-sweetened beverages in the past decades has paralleled the rise in obesity prevalence. Among three US cohorts, interactions between genetic susceptibility to obesity and sugar-sweetened beverages in relation to BMI and obesity were examined, and investigators found that genetic associations with increased BMI and obesity risk are pronounced with high intake of sugar-sweetened beverages [10]. Similar findings were observed in a recent study on Swedish adults [11].

In addition to sugar-sweetened beverages, coffee is among the most widely consumed beverages around the world. Regular coffee consumption has been associated with a reduced risk of several obesity-related diseases, such as type 2 diabetes, but the association between coffee consumption and obesity are not entirely consistent. A study on three US cohorts has found that high habitual coffee consumption may attenuate the genetic association with increased BMI and obesity risk [12].

The consumption of high-fat food may be an indicator of an unhealthy diet. In a study on three US cohorts, individuals with the *APOA2* CC genotype seem highly susceptible to increased BMI and obesity when they consume a high-saturated fat diet [13]. Foods become rich in fat after they are fried, and eating fried foods may result in high intake of high-fat foods. In a study on three US cohorts, a high frequency of fried food intake may amplify the genetic association with high BMI and obesity risk [14].

One previous study on 18 European cohorts tested whether a composite score representing healthy diet, which was calculated on the basis of whole grains, fish, fruits, vegetables, nuts/seeds, red/processed meats, sweets, sugar-sweetened beverages, and fried potatoes, modifies the associations of genetic variations, which were assessed in terms of the genetic risk scores of 32 BMI- and 14 waist–hip ratio-associated single nucleotide polymorphisms, with obesity traits [15]. Although the magnitudes of the reported interactions were small, this study suggested that the associations between genetic predisposition and obesity traits were strong with a healthy diet. One study on two US cohorts examined the interaction between adherence to healthy dietary patterns and genetic predisposition to

Table 1 Dietary factors that may interact with genetic susceptibility to obesity on adiposity in observational studies

Studies	Dietary factors	Genetic factors	Major findings
Qi *et al*. 2012 [10]	Sugar-sweetened beverages	A genetic risk score based on 32 BMI-associated loci	High consumption of sugar-sweetened beverages may amplify the genetic association with higher BMI and obesity risk
Brunkwall *et al*. 2016 [11]	Sugar-sweetened beverages	A genetic risk score based on 30 BMI-associated loci	The relation of sugar-sweetened beverages intake and BMI is strong in people genetically predisposed to obesity
Wang *et al*. 2017 [12]	Coffee	A genetic risk score based on 77 BMI-associated loci	High habitual coffee consumption may attenuate the genetic association with high BMI and obesity risk
Corella *et al*. 2009 [13]	Saturated fat	*APOA2*–265T>C polymorphism	Individuals with the *APOA2* CC genotype show increased susceptibility to increased BMI and obesity when they consume a high-saturated fat diet
Qi *et al*. 2014 [14]	Fried food	A genetic risk score based on 32 BMI-associated loci	Higher frequency of fried food consumption may amplify the genetic association with high BMI and obesity risk
Nettleton *et al*. 2015 [15]	A diet score based on whole grains, fish, fruits, vegetables, nuts/seeds (favorable) and red/processed meats, sweets, sugar-sweetened beverages, and fried potatoes (unfavorable)	A genetic risk score based on 18 WHR-associated loci	The associations between genetic predisposition and obesity traits were strong with a healthy diet
Wang *et al*. 2018 [16]	Two diet score: Alternate Healthy Eating Index 2010 and Dietary Approach to Stop Hypertension	A genetic risk score based on 77 BMI-associated loci	The association between a healthy diet and weight loss was strong in participants with a great genetic predisposition to obesity

obesity in relation to long-term weight change. The authors found that the association between a healthy diet, which was assessed by the Alternate Healthy Eating Index 2010 and Dietary Approach to Stop Hypertension, and long-term weight loss is strong in participants with a great genetic predisposition to obesity [16].

Evidence obtained in the US and Europe has suggested that genetic variants and particular dietary factors may interplay in relation to BMI and obesity. Adiposity may interact with genetic susceptibility on nonalcoholic fatty liver disease (NAFLD) and dyslipidemia, which are frequently associated with obesity and excessive calorie intake. Adiposity remarkably amplifies the effect of the *PNPLA3* I148M rs738409 variant associated with NAFLD [17], and this variant interacts with overweight and dietary intakes on fasting triglyceride levels [18].

The advantages of testing gene–diet interactions in observational studies include a large sample size, long follow-up periods, and generalizability of findings to general populations; however, results may be biased by confounding and reverse causation.

Evidence from diet interventions

Evidence-based prevention and intervention rely mainly on the statistical interpretation of data from randomized clinical trials in which the potential confounding effects are minimized. Therefore, gene–diet interaction in diet intervention trials on weight loss should be detected. Table 2 summarizes the studies on gene–diet interaction in randomized diet intervention trials published since 2011 [19−39].

The trial on Preventing Overweight Using Novel Dietary Strategies (Pounds Lost) comprised 811 overweight or obese adults who were assigned to 1 of 4 weight-loss diets varying in macronutrient contents for 2 years [40]. Investigators performed a series of analyses on

Table 2 Selected gene–diet interactions on obesity and related metabolic traits in randomized trials

Studies	Study design	Genetic factors	Major findings
Qi *et al*. 2011 [19]	*N* = 738; 2-y diet intervention	Diabetes-associated *IRS1* rs2943641	*IRS1* genetic variants modify effects of dietary carbohydrate on weight loss and insulin resistance
Erez *et al*. 2011 [20]	*N* = 322; 2-y diet intervention	Obesity-related *LEP* variants	*LEP* genotype is related to weight regain from 7–24 m
Mattei *et al*. 2012 [21]	*N* = 591; 2-y diet intervention	Diabetes-associated *TCF7L2* variant rs7903146	Dietary fat intake interacts with *TCF7L2* genotype in relation to changes in BMI, total fat mass, and trunk fat mass
Zhang *et al*. 2012 [22]	*N* = 742; 2-y diet intervention	Obesity-related *FTO* variant rs1558902	High-protein diet interacts with *FTO* genotype in relation to weight loss and improvement of body composition and fat distribution
Heni *et al*. 2012 [23]	*N* = 304; 9-m diet intervention	Diabetes-associated *TCF7L2* variant rs7903146	CC genotype is associated with great weight loss in participants with high fiber intake but not those with low fiber intake
Zhang *et al*. 2012 [24]	*N* = 734; 2-y diet intervention	Lipid metabolism-related *APOA5* variant rs964184	Dietary fat interacts with *APOA5* genotype in relation to 2-y changes in lipid profile
Zhang *et al*. 2012 [25]	*N* = 723; 2-y diet intervention	Hypertension-associated *NPY* variant rs16147	*NPY* genotype modifies effects of dietary fat on 2-y changes of blood pressure
Larsen *et al*. 2012 [26]	*N* = 742; 6-m diet intervention on weight loss maintenance	768 tag SNPs for nutrient-sensitive genes	Multiple interactions with GI or dietary protein on waist and fat mass regain
Qi *et al*. 2012 [27]	*N* = 737; 2-y diet intervention	Diabetes-related *GIPR* variant rs2287019	Dietary carbohydrate modified *GIPR* genotype effects on changes in body weight, fasting glucose, and insulin resistance
Xu *et al*. 2013 [28]	*N* = 734; 2-y diet intervention	*BCAA*-associated *PPM1K* SNP rs1440581	Dietary fat significantly modifies genetic effects on changes in weight and fasting insulin
Brahe *et al*. 2013 [29]	*N* = 841 (baseline); 6-m diet intervention on weight loss maintenance	240 tag SNPs for candidate genes	*LPIN1* SNP rs4315495 genotype interacts with dietary protein on change of TG concentration
McCaffery *et al*. 2013 [30]	*N* = 3899; 4-y lifestyle intervention in diabetic patients	Obesity-related variants	Variations in the *FTO* and *BDNF* loci are related to weight regain after weight loss
Pan *et al*. 2013 [31]	*N* = 3819; 2-y intervention; lifestyle modification and metformin	Obesity-related *MC4R* variants	rs17066866 is associated with less short-term (baseline to 6 m) and less long-term (baseline to 2 y) weight loss in the lifestyle intervention group but not in placebo group

(*Continued*)

Studies	Study design	Genetic factors	Major findings
Kostis *et al*. 2013 [32]	N = 722; 4-m intervention; diet and medication	21 SNPs related to hypertension, diabetes, or obesity	Multiple genotypes are related to change in blood pressures in response to diet intervention
Qi *et al*. 2013 [33]	POUNDS Lost: N = 738; 2-y diet intervention	Diabetes-associated *IRS1* rs2943641 and rs1522813	High-fat weight-loss diets may be more effective in the management of the metabolic syndrome compared with low-fat diets among individuals with the A-allele of the rs1522813 variant near *IRS1*
Mirzaei *et al*. 2014 [34]	N = 721; 2-y diet intervention	Circadian-related genes *CRY2* and *MTNR1B*	Variants in *CRY2* and *MTNR1B* may affect long-term changes in energy expenditure, and dietary fat intake may modify the genetic effects
Huang *et al*. 2015 [35]	N = 730; 2-y diet intervention	Iron homeostasis-related *PCSK7* variant	*PCSK7* genotypes may interact with dietary carbohydrate intake on changes in insulin sensitivity
Qi *et al*. 2015 [36]	POUNDS Lost: N = 732; 2-y diet intervention; DIRECT: N = 171; 2-y diet intervention	Cholesterol-related *CETP* variant	Individuals with the *CETP* rs3764261 CC genotype may derive great effects on raising HDL cholesterol and lowering triglycerides by choosing a low-carbohydrate/high-fat weight-loss diet instead of a low-fat diet
Zheng *et al*. 2015 [37]	N = 743; 2-y diet intervention	Obesity-associated *FTO* variant	Carriers of the risk alleles of rs1558902 benefit differently in improving insulin sensitivity by consuming high-fat weight-loss diets rather than low-fat diets
Lin *et al*. 2015 [38]	N = 723; 2-y diet intervention	Obesity-associated *NPY* variant	NPY rs16147 genotypes affect the change in abdominal adiposity in response to dietary interventions
Qi *et al*. 2015 [39]	N = 721; 2-y diet intervention	Three vitamin D metabolism-related variants	Individuals carrying the T allele of DHCR7 rs12785878 may benefit more in improvement of insulin resistance than non-carriers by consuming high-protein weight-loss diets

Abbreviations: BCAA, branched chain amino acid; GI, glycemic index; HDL, high-density lipoprotein cholesterol; m, month; SNP, single nucleotide polymorphism; TG, triglyceride; y, year.

gene–diet interactions in the POUNDS Lost trial [19,21,22,24,25,27,28,33–39]. For example, the *FTO* genetic variants, which are among the main culprits in determining genetic susceptibility to obesity and are highly expressed in the central nervous system, have been found to modify the effect of dietary protein intake or dietary fat intake on a series of obesity-related traits, such as weight loss, changes in body composition and fat distribution, and improvement of insulin resistance [22,37]. Insulin receptor substrate 1 (*IRS1*) gene has been associated with insulin resistance and hyperinsulinemia, and genetic variants in *IRS1* significantly interact with dietary fat intake in relation to weight loss, improvement in insulin resistance, and the management of the metabolic syndrome components in this trial [19,33].

Other studies have examined gene–diet interactions in randomized intervention trials [20,23,26,29–32]. The transcription factor 7-like 2 (*TCF7L2*) genetic variant rs7903146 interacts with dietary fiber intake in relation to weight loss in the Tübingen Lifestyle Intervention Program, a trial consisting of exercise and diet intervention with decreased intake of fat and increased intake of fibers (> 15 g of fiber per 1000 kcal) [23]. In the Diabetes Prevention Program, Pan *et al*. [31] found that the minor allele of *MC4R* rs17066866 is associated with less weight loss during 6 months and 2 years in the lifestyle intervention group that receives less fat and calories and exercises for a total of 150 min a week but not in the placebo group. However, identifying the confounding factors from interactions between lifestyle components (diet or exercise) and genotypes is difficult.

These findings from randomized intervention trials suggest that weight loss and related metabolic improvement can be conditional on different genetic backgrounds in response to diet interventions. One unique advantage of studies applying diet intervention trials to test gene–diet interactions is that they may provide direct evidence to instruct genetic-targeted diet modifications in future public health practice. However, most of existing diet intervention trials are relatively small in size, thereby limiting the power for the detection of moderate gene–diet interactions [4], and replication remains a major challenge in gene–diet interaction analyses in randomized trials.

Challenges and future prospects

Current gene–diet interaction findings clearly show that genes and diets unlikely separately affect obesity and related metabolic traits. Individuals with high genetic predisposition may reveal increased susceptibility to adverse health outcomes in response to unhealthy diets. Alternatively, healthy diets may counteract the negative effects associated with certain genetic predisposition.

Remarkable challenges still exist in this field. The sample size required to detect a multiplicative interaction effect of two variables is at least four times the sample size that is needed to evaluate the main effect of each of the variables. Unless the interactions are strong, the occurrence of false-negative findings about such interactions is a concern in individual studies [7]. The replication of findings is necessary to interpret gene–diet interactions. Therefore, collaborative individual well-designed studies should be performed to increase the power of analyses and search consistent results across different studies. New statistical approaches are required to establish biologically functional relevance for the observed statistically significant gene–diet interactions. The majority of current gene–diet interaction analyses apply the identified genetic variables from the GWAS. Emerging genome-wide approaches facilitate studies on mining interactions in genome-wide data and exploring biological pathways [41].

Obesity and related metabolic diseases can be prevented by adhering healthy lifestyle and diet habits. Gene–diet interaction studies help accelerate efficient diet interventions in a personalized manner, which is different from the traditional one-size-fits-all approach [42]. Although genomic information is not generally applied to predict diseases, it can be used with other risk factors to screen and classify high-risk populations to tailored interventions.

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Compliance with ethics guidelines

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References

1. Makris A, Foster GD. Dietary approaches to the treatment of obesity. Psychiatr Clin North Am 2011; 34(4): 813–827
2. Malik VS, Hu FB. Popular weight-loss diets: from evidence to practice. Nat Clin Pract Cardiovasc Med 2007; 4(1): 34–41
3. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009; 360(9): 859–873
4. Qi L. Gene–diet interactions in complex disease: current findings and relevance for public health. Curr Nutr Rep 2012; 1(4): 222–227
5. Qi L, Cho YA. Gene–environment interaction and obesity. Nutr Rev 2008; 66(12): 684–694
6. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Mägi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segrè AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpeläinen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proença C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, den Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grässler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ,

O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010; 42(11): 937–948

7. Hunter DJ. Gene–environment interactions in human diseases. Nat Rev Genet 2005; 6(4): 287–298
8. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962; 14: 353–362
9. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. Int J Obes 2008; 32(11): 1611–1617
10. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, Ridker PM, Hunter DJ, Willett WC, Rimm EB, Chasman DI, Hu FB, Qi L. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012; 367(15): 1387–1396
11. Brunkwall L, Chen Y, Hindy G, Rukh G, Ericson U, Barroso I, Johansson I, Franks PW, Orho-Melander M, Renström F. Sugar-sweetened beverage consumption and genetic predisposition to obesity in 2 Swedish cohorts. Am J Clin Nutr 2016; 104(3): 809–815
12. Wang T, Huang T, Kang JH, Zheng Y, Jensen MK, Wiggs JL, Pasquale LR, Fuchs CS, Campos H, Rimm EB, Willett WC, Hu FB, Qi L. Habitual coffee consumption and genetic predisposition to obesity: gene–diet interaction analyses in three US prospective studies. BMC Med 2017; 15(1): 97
13. Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, Tucker K, Lai CQ, Parnell LD, Coltell O, Lee YC, Ordovas JM. APOA2, dietary fat, and body mass index: replication of a gene–diet interaction in 3 independent populations. Arch Intern Med 2009; 169(20): 1897–1906
14. Qi Q, Chu AY, Kang JH, Huang J, Rose LM, Jensen MK, Liang L, Curhan GC, Pasquale LR, Wiggs JL, De Vivo I, Chan AT, Choi HK, Tamimi RM, Ridker PM, Hunter DJ, Willett WC, Rimm EB, Chasman DI, Hu FB, Qi L. Fried food consumption, genetic risk, and body mass index: gene–diet interaction analysis in three US cohort studies. BMJ 2014; 348: g1610
15. Nettleton JA, Follis JL, Ngwa JS, Smith CE, Ahmad S, Tanaka T, Wojczynski MK, Voortman T, Lemaitre RN, Kristiansson K, Nuotio ML, Houston DK, Perälä MM, Qi Q, Sonestedt E, Manichaikul A, Kanoni S, Ganna A, Mikkilä V, North KE, Siscovick DS, Harald K, Mckeown NM, Johansson I, Rissanen H, Liu Y, Lahti J, Hu FB, Bandinelli S, Rukh G, Rich S, Booij L, Dmitriou M, Ax E, Raitakari O, Mukamal K, Männistö S, Hallmans G, Jula A, Ericson U, Jacobs DR Jr, Van Rooij FJ, Deloukas P, Sjögren P, Kähönen M, Djousse L, Perola M, Barroso I, Hofman A, Stirrups K, Viikari J, Uitterlinden AG, Kalafati IP, Franco OH, Mozaffarian D, Salomaa V, Borecki IB, Knekt P, Kritchevsky SB, Eriksson JG, Dedoussis GV, Qi L, Ferrucci L, Orho-Melander M, Zillikens MC, Ingelsson E, Lehtimäki T, Renström F, Cupples LA, Loos RJ, Franks PW. Gene × dietary pattern interactions in obesity: analysis of up to 68 317 adults of European ancestry. Hum Mol Genet 2015; 24(16): 4728–4738
16. Wang T, Heianza Y, Sun D, Huang T, Ma W, Rimm EB, Manson JE, Hu FB, Willett WC, Qi L. Improving adherence to healthy dietary patterns, genetic risk, and long term weight gain: gene–diet interaction analysis in two prospective cohort studies. BMJ 2018; 360: j5644
17. Stender S, Kozlitina J, Nordestgaard BG, Tybjærg-Hansen A, Hobbs HH, Cohen JC. Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. Nat Genet 2017; 49(6): 842–847
18. Stojkovic IA, Ericson U, Rukh G, Riddestråle M, Romeo S, Orho-Melander M. The PNPLA3 Ile148Met interacts with overweight and dietary intakes on fasting triglyceride levels. Genes Nutr 2014; 9(2): 388
19. Qi Q, Bray GA, Smith SR, Hu FB, Sacks FM, Qi L. Insulin receptor substrate 1 gene variation modifies insulin resistance response to weight-loss diets in a 2-year randomized trial: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. Circulation 2011; 124(5): 563–571
20. Erez G, Tirosh A, Rudich A, Meiner V, Schwarzfuchs D, Sharon N, Shpitzen S, Blüher M, Stumvoll M, Thiery J, Fiedler GM, Friedlander Y, Leiterstdorf E, Shai I. Phenotypic and genetic variation in leptin as determinants of weight regain. Int J Obes 2011; 35(6): 785–792
21. Mattei J, Qi Q, Hu FB, Sacks FM, Qi L. TCF7L2 genetic variants modulate the effect of dietary fat intake on changes in body composition during a weight-loss intervention. Am J Clin Nutr 2012; 96(5): 1129–1136
22. Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. Diabetes 2012; 61(11): 3005–3011
23. Heni M, Herzberg-Schäfer S, Machicao F, Häring HU, Fritsche A.

Dietary fiber intake modulates the association between variants in TCF7L2 and weight loss during a lifestyle intervention. Diabetes Care 2012; 35(3): e24

24. Zhang X, Qi Q, Bray GA, Hu FB, Sacks FM, Qi L. APOA5 genotype modulates 2-y changes in lipid profile in response to weight-loss diet intervention: the Pounds Lost Trial. Am J Clin Nutr 2012; 96(4): 917–922
25. Zhang X, Qi Q, Liang J, Hu FB, Sacks FM, Qi L. Neuropeptide Y promoter polymorphism modifies effects of a weight-loss diet on 2-year changes of blood pressure: the preventing overweight using novel dietary strategies trial. Hypertension 2012; 60(5): 1169–1175
26. Larsen LH, Angquist L, Vimaleswaran KS, Hager J, Viguerie N, Loos RJ, Handjieva-Darlenska T, Jebb SA, Kunesova M, Larsen TM, Martinez JA, Papadaki A, Pfeiffer AF, van Baak MA, Sørensen TI, Holst C, Langin D, Astrup A, Saris WH. Analyses of single nucleotide polymorphisms in selected nutrient-sensitive genes in weight-regain prevention: the DIOGENES study. Am J Clin Nutr 2012; 95(5): 1254–1260
27. Qi Q, Bray GA, Hu FB, Sacks FM, Qi L. Weight-loss diets modify glucose-dependent insulinotropic polypeptide receptor rs2287019 genotype effects on changes in body weight, fasting glucose, and insulin resistance: the Preventing Overweight Using Novel Dietary Strategies trial. Am J Clin Nutr 2012; 95(2): 506–513
28. Xu M, Qi Q, Liang J, Bray GA, Hu FB, Sacks FM, Qi L. Genetic determinant for amino acid metabolites and changes in body weight and insulin resistance in response to weight-loss diets: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. Circulation 2013; 127(12): 1283–1289
29. Brahe LK, Ängquist L, Larsen LH, Vimaleswaran KS, Hager J, Viguerie N, Loos RJ, Handjieva-Darlenska T, Jebb SA, Hlavaty P, Larsen TM, Martinez JA, Papadaki A, Pfeiffer AF, van Baak MA, Sørensen TI, Holst C, Langin D, Astrup A, Saris WH. Influence of SNPs in nutrient-sensitive candidate genes and gene–diet interactions on blood lipids: the DiOGenes study. Br J Nutr 2013; 110(5): 790–796
30. McCaffery JM, Papandonatos GD, Huggins GS, Peter I, Kahn SE, Knowler WC, Hudnall GE, Lipkin EW, Kitabchi AE, Wagenknecht LE, Wing RR. FTO predicts weight regain in the Look AHEAD clinical trial. Int J Obes 2013; 37(12): 1545–1552
31. Pan Q, Delahanty LM, Jablonski KA, Knowler WC, Kahn SE, Florez JC, Franks PW; Diabetes Prevention Program Research Group. Variation at the melanocortin 4 receptor gene and response to weight-loss interventions in the diabetes prevention program. Obesity (Silver Spring) 2013; 21(9): E520–E526
32. Kostis WJ, Cabrera J, Hooper WC, Whelton PK, Espeland MA, Cosgrove NM, Cheng JQ, Deng Y, De Staerck C, Pyle M, Maruthur N, Reyes I, Anderson CA, Liu J, Kostis JB. Relationships between selected gene polymorphisms and blood pressure sensitivity to weight loss in elderly persons with hypertension. Hypertension 2013; 61(4): 857–863
33. Qi Q, Xu M, Wu H, Liang L, Champagne CM, Bray GA, Sacks FM, Qi L. IRS1 genotype modulates metabolic syndrome reversion in response to 2-year weight-loss diet intervention: the POUNDS LOST trial. Diabetes Care 2013; 36(11): 3442–3447
34. Mirzaei K, Xu M, Qi Q, de Jonge L, Bray GA, Sacks F, Qi L. Variants in glucose- and circadian rhythm-related genes affect the response of energy expenditure to weight-loss diets: the POUNDS LOST Trial. Am J Clin Nutr 2014; 99(2): 392–399
35. Huang T, Huang J, Qi Q, Li Y, Bray GA, Rood J, Sacks FM, Qi L. PCSK7 genotype modifies effect of a weight-loss diet on 2-year changes of insulin resistance: the POUNDS LOST trial. Diabetes Care 2015; 38(3): 439–444
36. Qi Q, Durst R, Schwarzfuchs D, Leitersdorf E, Shpitzen S, Li Y, Wu H, Champagne CM, Hu FB, Stampfer MJ, Bray GA, Sacks FM, Shai I, Qi L. CETP genotype and changes in lipid levels in response to weight-loss diet intervention in the POUNDS LOST and DIRECT randomized trials. J Lipid Res 2015; 56(3): 713–721
37. Zheng Y, Huang T, Zhang X, Rood J, Bray GA, Sacks FM, Qi L. Dietary fat modifies the effects of FTO genotype on changes in insulin sensitivity. J Nutr 2015; 145(5): 977–982
38. Lin X, Qi Q, Zheng Y, Huang T, Lathrop M, Zelenika D, Bray GA, Sacks FM, Liang L, Qi L. Neuropeptide Y genotype, central obesity, and abdominal fat distribution: the POUNDS LOST trial. Am J Clin Nutr 2015; 102(2): 514–519
39. Qi Q, Zheng Y, Huang T, Rood J, Bray GA, Sacks FM, Qi L. Vitamin D metabolism-related genetic variants, dietary protein intake and improvement of insulin resistance in a 2 year weight-loss trial: POUNDS Lost. Diabetologia 2015; 58(12): 2791–2799
40. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009; 360(9): 859–873
41. Thomas D. Gene – environment-wide association studies: emerging approaches. Nat Rev Genet 2010; 11(4): 259–272
42. Offit K. Personalized medicine: new genomics, old lessons. Hum Genet 2011; 130(1): 3–14