Acta Biomed 2020; Vol. 91, Supplement 13: e2020011 DOI: 10.23750/abm.v91i13-S.10584

Review

Genetic test for the prescription of diets in support of physical activity

Zakira Naureen,[1] Giacinto Abele Donato Miggiano,[2] Barbara Aquilanti,[3] Valeria Velluti,[3] Giuseppina Matera,[3] Lucilla Gagliardi,[3] Alessandra Zulian,[4] Roberta Romanelli,[4] Matteo Bertelli[4,5,6]

[1] Department of Biological Sciences and Chemistry, College of Arts and Sciences, University of Nizwa, Nizwa, Oman; [2] Human Nutrition Research Center, Sacro Cuore Catholic University, Rome, Italy; [3] UOC Nutrizione Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [4] MAGI'S LAB, Rovereto (TN), Italy; [5] MAGI EUREGIO, Bolzano, Italy; [6] EBTNA-LAB, Rovereto (TN), Italy

Abstract. Owing to the fields of nutrigenetics and nutrigenomics today we can think of devising approaches to optimize health, delay onset of diseases and reduce its severity according to our genetic blue print. However this requires a deep understanding of nutritional impact on expression of genes that may result in a specific phenotype. The extensive research and observational studies during last two decades reporting interactions between genes, diet and physical activity suggest a cross talk between various genetic and environmental factors and lifestyle interventions. Although considerable efforts have been made in unraveling the mechanisms of gene-diet interactions the scientific evidences behind developing commercial genetic tests for providing personalized nutrition recommendations are still scarce. In this scenario the current mini-review aims to provide useful insights into salient feature of nutrition based genetic research and its commercial application and the ethical issue and concerns related to its outcome.(www.actabiomedica.it)

Key words: nutrigenetics, nutrigenomics, direct to consumer test, personalized nutrition, obesity, physical activity

Introduction

The notion that each of us has an exclusive nutrition blueprint within our genes is a scrumptious concept. Nutrients can indeed influence phenotypic expression of an individual's genotype by modifying gene expression at pre- and post-transcriptional and translational levels. This might result into improving health of an individual or, on the other hand, may affect the health in a negative manner. On the contrary there are certain genes that may give preferential benefit to intake of some of the nutrients while adversely affecting the consumptions of other. The complexity and girth of this scenario led to the development of two interesting scientific fields, nutrigenetics and nutrigenomics.

Nutrigenetics and nutrigenomics are defined as the branches of science dealing with the effect of genetic variation on nutritional response and the function of nutrients and bioactive food compounds in influencing gene expression, respectively (1-3). The wealth of genomic information coupled with high-throughput 'omics' technologies facilitates the acquisition of in-depth knowledge of nutrient-gene interactions that ultimately lead to development of personalized nutrition approaches for good health and disease prevention (4-6). There are three fundamental factors underlying nutrigenetics and nutrigenomics. Genomic diversity with respect to ethnicity that affects nutrient bioavailability and metabolism, choice and availability of food depending on cultural, socioeconomical, geographical

and sense of taste of an individual and malnutrition that can affect gene expression and pose threats to genome stability by paving the way for mutations in gene sequences or causing chromosomal aberrations resulting into abnormal gene dosage and corresponding adverse phenotypes (1-6).

Although the terms nutrigenomics and nutrigenetics look similar and are closely related, these terms are not interchangeable as nutrigenetics investigates the effect of inherited genetic traits or their variants and mutations on micronutrient uptake and metabolism while nutrigenomics is the interconnection between genome and diet which explains the nutritional effects on transcription, translation, proteomic, metabolomics changes and the variation in dietary factors due to individual genetic background (7, 8). Due to advancement in science now it is possible and affordable for individuals to get information about possibility of having alterations in genes involved in nutrient metabolism and pathways requiring micronutrients as cofactors, due to point or frameshift mutations or copy number variations (9). Age and gender may as well contribute to gene-diet interactions involved in micronutrient uptake for health maintenance (10). Hence the key challenge is to utilize this information to provide reliable and predictable personalized dietary recommendations for optimum health and wellbeing.

Another important emerging facet of gene-diet-interaction is involvement of epigenetic with the potential for both intra- and transgenerational effects (11,12). Epigenetics refers to regulatory mechanisms that play an important role in switching genes on and off thus having a strong impact on growth and development with epigenetic controls being lost during diseases such as cancer. Whereas epigenomics involves analysis of epigenetic changes in a cell or entire organism. Diet has a special perspective in this regard in the sense that either alone or in combination with confounding environmental factors it may switch certain genes on or off. Consequently , this may either lead to uncontrolled growth leading to cancer or predisposition to and susceptibility towards developing diseases later on in life (13,14). Thence the epigenome is the global epigenetic pattern that is heritable and modifiable by diet. The gene-specific modifications like DNA methylation, histone modifications and chromatin remodeling regulate the expression of house-keeping genes and suppress the expression of parasitic transposons (1,2,14).

This mini review aims to provides various perspectives on nutrigenomics and nutrigenetics and the use of technologies to unravel gene diet-interactions and their underlying mechanisms that result into inter-individual variations in response to the same nutritional intakes.

Genetic variation/ polymorphisms affecting response to dietary intake

The term "personalized nutrition" is not a new concept. We have examples from inborn errors of metabolism that the nutrition regime can be customized for a healthy life. These inborn errors of metabolism are a consequence of genetic variations in the genes coding specific metabolic enzymes. Unavailability or non-functionality of these enzymes leads to metabolic problems. These variations can result in gene-diet-interactions and alter the nutrient requirements and the metabolism (4,5).

Classical examples of such single gene- diet- interactions affecting the response to dietary intake are phenylketonuria and lactose intolerance. Phenylketonuria is an autosomal recessive disorder caused by mutations in gene encoding a key hepatic enzyme phenyl alanine hydroxylase. Individuals having phenylketonuria need to avoid foods containing amino acid phenyl alanine as they lack or have very low activity of phenyl alanine hydroxylase to metabolize this amino acid (6). Another common example is the autosomal recessive lactose intolerance. This phenotype is caused by a point mutation in the lactase gene (*LCT*) that results into a T to C transition leading to the malfunctioning or absent lactase. Consequently, individuals that harbor this mutation are unable to digest lactose.

Besides these straight forward genetic interactions involving single genes and diet there are more complex polygenic interactions and multifactorial etiologies, such as obesity, cardiovascular disease (CVD), type 2 diabetes and cancer (1,2). Such disorders involve interactions among many genes and can be influenced by several dietary exposures. For instance multiple ge-

netic variants have been linked with an increased risk of obesity such as fat mass and obesity associated gene (*FTO*, rs9939609), genes encoding peroxisome proliferator-activated receptor protein, uncoupling proteins (UCP1 and UCP3), leptin receptor and melanocortin 4 receptor (15-18).

In case of coronary artery disease variations in genes involved in lipid metabolism such as cholesteryl ester transfer protein (*CETP*); lipoprotein lipase (*LPL*), apolipoprotein E (*APOE*), low density lipoprotein receptor (*LDLR*) affect the uptake and catabolism of cholesterol and other lipids thus causing fat deposition in the arteries (atherosclerosis) that can be dangerous for health (19-22). Other genetic variants may be responsible for diabetes, cancer and other diseases (23-25). Another important example of metabolic pathways affected by genetic variants in genes encoding metabolic enzymes regards the variants that can be present in methyl tetrahydrofolate reductase gene (*MTHFR*). Two common variants in *MTHFR* C677T and A1298C have a minor allele frequency of 25% in Hispanic people and 10% in North American Caucasians. Both cause homocystenemia that eventually might result in birth defects, encephalopathies and glaucoma (26).

At present, there are many examples of how nutrigenomics is studying these complex disorders. One of those studies analyzed the involvement of genetic variants in the gene *CYP1A2* encoding a caffeine-metabolizing enzyme in CVD (27). The study reported that high caffeine consumption may be associated with an increased risk of CVD in individuals carrying the "slow" caffeine metabolizing variant of the gene. On the contrary, individuals having fast coffee metabolizing genotype have a protective effect on moderate coffee consumption (27).

Substantial efforts have also been made in determining genetic variants in metabolic enzymes to devise effective optimal dietary regimes to prevent obesity, which may be a major contributory factor in chronic diseases such as CVD and type 2 diabetes. One example are the genetic variations in the apolipoprotein A2 gene (*APOA2*) that predisposes to obesity via altered energy intake (28). Individuals of Chinese and Asian-Indian origin with a specific variant in *APOA2* are at increased risk of developing obesity when saturated fat intake is high, but not when saturated fat intake is low (28). Similar studies were replicated in a Mediterranean population from the southeast of Spain (29).

Additionally, polymorphisms in genes linked with the metabolism of vitamin C, D, B_{12} and iron, have been shown to predispose to risk of suboptimal or deficient blood levels of these nutrients leading to several abnormalities and diseases (30-33).

Despite the fact that these studies and many other similar studies provide strong evidence of benefits from personalised nutrition further research is required to deepen our knowledge of genetic association with dietary intake and physical activities in various ethnic groups (34,35). One of the ultimate objectives of nutrigenetics and nutrigenomics in this scenario is the development of genetic tests based on genetic markers. Research has shown that DNA-based personalised nutrition advice is taken more seriously and more willingly by the people in terms of alteration in behaviour and adapting to healthy lifestyle pattern (34,35).

Nutrigenetics-based personalized nutrition

Given the complexity of the matter, there is not a single definition for personalized nutrition, also called precision or "tailored" nutrition (36). Its aim is to give dietary advice in order to improve dietary habits (37). Personalized nutrition practices may involve direct face to face consultations or web based computer-generated nutrition advice (38). In this context, genetic-based personalized nutrition is a healthy tailored dietary recommendation based on genetic information collected by genetic testing (39). These data are coupled with lifestyle data such as age, gender, weight, height and clinical history for underlying diseases, food allergies, dietary habits and physical activity. Some centers also take into account gut microbiota (40). In fact, it can alter genetic expression in response to dietary intake and physical activity (40). Hence, personalized nutrition is a complex field (41).

Scientific validity and evidence for genotype-based dietary advice

In principle, to avoid misuse of the genetic information and protect the basic human rights of safety,

privacy and well-being there should be clear guidelines to follow in nutrigenetics. Furthermore, these genetic findings should be translated carefully keeping in view the available scientific evidence. A draft framework for assessing the significance and practical application of the nutrigenetic knowledge was presented by Grimaldi et al (42). They proposed that based on this framework, transparent and scientifically valid guidelines might be developed for nutrigenetic testing for public.

They further added that genetic testing is mainly an unregulated market in the sense that they provide insufficient descriptions of results and draw inferences which lack of scientific backing (43-48). For instance, scientific studies addressing gene-diet interactions are mainly based on observations made for a group of individuals of a specific ethnic group or with mixed ethnicity. The results presented by a study are specific for that particular study group and cannot be directly applied to individuals with different ethnicity, unless these results are replicated in different ethnic groups with people having different life styles and dietary habits. This is due to the fact that the overall effect of confounding factors on an individual phenotype is far greater than a trend observed in a group of people. Besides that, diets prescribed on the basis of a single gene variant may also lack scientific backing. In fact, the overall contribution of a single gene in phenotypic expression is minimal as compared to multiple genetic variants and their interactions with each other (42). Therefore, the best personalized nutritional advice can be given only on the basis of a polygenic profile, phenotype characterization, health status, food choices, lifestyle, environmental, cultural and economic factors (43). To overcome these differences, dietary reference values have been developed to set safe limits for nutrients based on age, gender and physiological state (49-51). They are designed to meet the requirement of 97.5% of the population. This implicates that although these reference values cover the dietary requirements of most of the people some individuals may remain uncovered. In this context, EU developed a strategy to harmonize the nutrient recommendations throughout EU member states taking into account vulnerable groups and consumer satisfaction (52).

Interactions between diet and genetic variants

Wrong dietary habits such as high intake of sugars, fats, alcohol and reduced intake of vegetables and fruits may predispose to the acquisition of non-communicable diseases such as CVD, hypertension, diabetes, cancer and obesity (53).

Several epidemiological studies have consistently shown that high intake of sugar sweetened beverages (54-56), fried food (57) and sedentary life style are particular risk factor for obesity among adults and children due to their complex interaction with genetic variants associated with obesity (58-61).

Several genome wide association studies have assessed the association of genetic polymorphisms with metabolic pathways (62). For instance, clinically significant interactions have been observed among the *APOA2* 2265T>C variant and saturated fats intake and BMI (42); *MTHFR* gene variants and homocyteine levels (26,61-66); *CYP1A2* genetic variants and hypertensive response to caffeine consumption.

Genome wide association and linkage studies have added more than 600 genetic variants and chromosomal regions to the repertoire of genetic factors associated with obesity, body weight, body mass index, body fat composition and distribution, energy expenditure and fuel oxidation and various other phenotypic features linked with nutrition (67-83). One of the first genetic variants associated with obesity was a single nucleotide polymorphism in the *FTO* gene. This variant affects body weight and body composition and carriers having *FTO* rs9939609 *AA* genotype are more likely to be obese as compared to non-carriers (71). Although this variant is the strongest risk factor associated with polygenic obesity, its effect can be modified by either physical activity or reduction in energy intake, providing an excellent example of cross talk between genetic variants and life style interventions (84). In addition to that another study revealed that patients carrying variant alleles of the *FTO* rs9939609 and *MC4R* rs17782313 are at a higher risk of type 2 diabetes mellitus (73). This implicates that the genetic variants can either affect the phenotype alone or in association with other genetic variants present in other loci or by complex interactions between genetic variants and environmental factors.

Genes and their polymorphs associated with obesity

One of the best method to achieve healthy weight loss is to create a calorie deficit by burning more calories than what we intake through diet. This method involves extensive and vigorous exercise or physical activity. On the other hand, intake of low calories with a more satiating diet may also result in weight loss in association with physical activity (67,81,83). Several genes have been reported to be linked with weight loss in response to hypocaloric diet coupled with physical activity. These genes mainly encodes important enzymes regulating lipid metabolism, adipogenesis, carbohydrate metabolism, circadian clock, energy intake and expenditure, appetite control, thermogenesis and cell differentiation (67-76). Furthermore, genetic variants in taste-, olfactory- and texture-related genes can influence sensitivity and preferences for certain food, thereby affecting the susceptibility towards nutrition-induced obesity (71). The key genetic variants that influence metabolic processes involved in increasing the risk of obesity and obesity-related diseases are *FTO, ADIPOQ, LEP, LEPR, INSIG2, MC4R, PCSK1, PPARG, ADBR2, ADBR3, GHRL, PPARγ, FABP2, APOA5, APOA1, LIPC, CETP, MTNR1B, NPY, GIPR, IRS1, TCF7L2, PCSK1* (84-120). The encoded proteins and their metabolic functions are presented in Table 1.

Genes and physical activity

Physical activity levels and intensity play an important role in moderating the risk of weight gain, in both weight loss program and in prevention of weight regain (121). Physical activity is a modifiable life style and is associated with cardio-metabolic outcomes, including obesity, type 2 diabetes, and cardiovascular diseases (122,123). A recent study by Goryakin et al., reported that more than half of the Italian population does not meet the least moderate activity threshold set by world health organization despite the fact that the government has passed several health policies for the promotion of active transport, mass media campaigns, physical activity in primary care, school-based interventions and mobile apps in order to promote exercise and physical activity (124). Another study in 2015 has highlighted that only 20.8% of the US population meets the US national guidelines for physical activity while 50.8% of all adults do not meet those guidelines (125). In this context, approximately 35% of the mortality due to coronary heart disease has been attributed to insufficient physical activity (126), leading to the estimated $117 billion health care expenditures annually in the US (127).

Given the importance of physical activity many research reports based on twin studies (128), heritage analysis (129-134), linkage studies (135-139), genome wide association studies have been dedicated to unravel the genetic variants associated with physical activity (140-143). Genes that have been consistently associated with physical activity are *FTO*, *ANKRD6*, *IL15R*, *PPARD*, *LEPR*, *CASR*, *PAPSS2*, *DRD2*, *GABRG3*, *ACE*, *MC4R* (137, 144-151). The names, functions and notable variants of these genes have been listed in Table 2.

A cross talk between genes, diet and physical activity for weight management

Genetic polymorphisms linked to obesity may exert their effects by influencing physical activity and, on the other hand, physically active life style may reduce the risk of obesity. Current evidences have shown that physical activity can modulate heritability estimates for obesity-related traits (125). For instance a study revealed significantly strong interactions between *FTO* intron 1 and physical activity in 16 independent cross sectional and interventional studies carried out in adults and children with European, African and East African origin (19, 127). In addition to this, a recent meta-analysis in individuals of European ancestry (sample size: 111421) proved a significant physical activity-genetic risk score (GRS) interaction with respect to 12 obesity predisposing polymorphism. The study indicated that this physical activity-GRS association is more evident in subjects living in North America (60).

Another meta-analysis on 218166 adults and 19268 children revealed that greater leisure time physical activity attenuated the effects of *FTO* vari-

Table 1. Genes and their respective polymorphisms related to obesity and fat metabolism

Gene (OMIM ID)	Full name	SNP ID	Association	Reference
FTO	Alpha-ketoglutarate dependent dioxygenase	rs9939609 rs1558902 rs8050136	Stimulation of food consumption	84-89
ADIPOQ	Adipocyte-, C1q-, and collagen domain-containing	rs1501299	Energy expenditure	90
LEP	Leptin	164160	Appetite regulation	91
LEPR	Leptin receptor	rs1805094		92
INSIG2	Insulin-induced gene 2	rs7566605	Regulation of cholesterol and fatty acid synthesis	93,94
MC4R	Melanocortin 4 receptor	rs17782313 rs17066866 rs1943226 rs11875096 rs1943224 rs7235242 rs11872992 rs8093815 rs17066856 rs17066836 rs1943227 rs1943218 rs17066829 rs9966412 rs17066859 rs9965495 rs12970134 rs17700633 rs11873305 rs8091237 rs7240064	Energy homeostasis, appetite regulation	95,96
PCSK1	Proprotein convertase subtilisin/kexin type 1	rs236918	Insulin resistance	97
PPARG	Peroxisome proliferator-activated receptor gamma	rs1801282	Increased BMI	98,99
ADBR2	Adeno receptor beta2	rs1042714 rs1042713	Adaptive thermogenesis	100, 101
ADBR3	Adeno receptor beta 3	rs4994		102,103,104
GHRL	Ghrelin	rs696217	Appetite regulation	105
FABP2	Fatty acid binding protein 2	rs1799883	Fatty acid uptake	107
APOA5	Apolipoprotein A5	rs964184 rs662799	Lipoprotein metabolism	108,109
APOA1	Apolipoprotein A1	rs670		110
LIPC	Lipase C hepatic type	rs2070895		111
CETP	Cholesteryl ester transfer protein	rs3764261		112

(continued on next page)

Table 1 ***(continued)*****.** Genes and their respective polymorphisms related to obesity and fat metabolism

Gene (OMIM ID)	Full name	SNP ID	Association	Reference
MT-NR1B	Melatonin receptor 1B	rs10830963	Appetite regulation	113,114
NPY	Neuropeptide Y	rs16147		115
GIPR	Gastric inhibitory polypeptide receptor	rs2287019	Insulin signaling	116
IRS1	Insulin receptor substrate 1	rs1522813 rs2943641		117,118
TCF7L2	Transcrption factor 7 like 2	rs12255372 rs7903146	Blood glucose homeostasis	119
PCSK1	Proprotein convertase subtilisin/Kexin type 1	rs6232 rs6234	Energy metabolism	120,121

ants, however, prolonged sedentary periods, such as watching TV, enhanced genetic predisposition to elevated adiposity (152). Moreover, Rankinen et al., reported that genetic association of *FTO* with BMI was strengthened by prolonged sedentary periods of watching TV in both men and women (153). Similar finding were reported by in another UK Biobank study with large sample size (154). They reported a strong genetic association with sedentary life style and risk of obesity which was worsened by inadequate sleep (154). The Diabetes Prevention Program in the US reported a strong interaction between FTO and a 1-y lifestyle intervention regime of physical activity, diet, and weight loss with respect to subcutaneous fat area among 869 individuals (155). They found the minor allele of the FTO variant is associated with increased subcutaneous fat area in the control group as compared to the lifestyle intervention group (155). Similarly a recent study indicated that physical activity combined with vegetarian diet can reduce the increased BMI caused by susceptibility due to *FTO* rs3751812 minor allele (156). Other physical activity-associated genes that can respond to dietary intake are genes involved in muscle structure and strength. A study in 461 European American adults showed the association of ACE I/D polymorphism rs4340 with a weekly walking distance of approximately 8 Km, ultimately reducing the BMI (157).

The aforementioned studies are a few examples of cross talk between genetic factors governing obesity and physical exercise. It can be concluded here that although genetic factors predispose to increased risk of obesity the environmental, behavioral, socioeconomic, psychological factors that contribute to overall life style determine the overall phenotype of an individual. Physical activity in this regard plays a vital role. Several studies have shown the importance of diet coupled with physical activity in maintaining a healthy weight. However there is no such 'one size fit for all' diet that can meet the dietary requirements of people belonging to various ethnic groups that keeps the obesity at bay without the need of physical activity.

Commercial genetic testing for personalized diet recommendations

Two types of genetic tests are basically carried out in commercial settings i.e. laboratory developed tests and direct to consumer tests (DTC). Both of these tests are used to identify genetic factors contributing to health related issues and to provide dietary recommendations. The DTC testing industry provides individuals an easy access to their own genetic information.

Table 2. Genes with their SNPs that influence metabolism of specific food and nutrients with a major impact on health status

Gene (OMIM ID)	Full name	SNP ID (risk allele)	SNP-associated phenotype	Diet intervention	Reference
MCM6 (*601806)	Minichromosome maintenance complex component 6	rs4988235 C>T (C) rs182549 G>A (G) rs145946881 G>C (G)	Lactose intolerance, adult type (#223100)	Avoid milk and its derivatives with high content of lactose	OMIM
HLA-DQA1 (*146880)	Major histocompatibility complex, class II, DQ alpha 1	rs2187668 C>T (C) rs2395182 G>T (G) rs4639334 G>A (G) rs4713586 A>G (G) rs7454108 T>C (C) rs7775228 T>C (C)	Susceptibility to celiac disease 1 (#212750)	Avoid foods containing gluten	
HLA-DQB1 (*604305)	Major histocompatibility complex, class II, DQ beta 1			Avoid foods containing gluten	
HJV (*608374)	Hemojuvelin BMP co-receptor	rs74315323 C>A rs74315324 G>A rs74315325 A>T rs74315326 A>G rs28940586 A>C,G rs74315327 A>G rs121434374 G>C,T rs786205063 $(GA)_3$G>GAG rs121434375 T>A	Hemochromatosis, type 2A (#602390)	Avoid iron-rich foods	
SLC40A1 (OMIM *604653)	Solute carrier family 40 member 1	rs104893662 T>A,G rs28939076 G>T rs878854984 $(CAA)_4$>$(CAA)_3$,$(CAA)_5$ rs104893663 T>A,C rs104893670 C>A,T rs104893671 C>A rs104893672 T>A rs104893673 C>A rs104893664 C>T	Hemochromatosis, type 4		
HFE (*613609)	Homeostatic iron regulator	rs1800562 G>A rs1799945 C>G,T rs1800730 A>T rs1800758 G>A rs28934889 G>A rs111033557 G>A rs28934595 A>C rs111033558 G>C,T rs28934596 T>C rs28934597 G>C rs111033563 A>C	Hemochromatosis		

(continued on next page)

Table 2 ***(continued)*****.** Genes with their SNPs that influence metabolism of specific food and nutrients with a major impact on health status

Gene (OMIM ID)	Full name	SNP ID (risk allele)	SNP-associated phenotype	Diet intervention	Reference
TFR2	Transferrin receptor 2	rs80338880 G>C rs80338877 $(G)_5$>$(G)_6$ rs80338879 A>T rs41303501 C>T rs80338889 T>C,G	Hemochromatosis, type 3		OMIM
FTH1	Ferritin heavy chain 1	rs387906549 T>A	Hemochromatosis, type 5		
HAMP (*606464)	Hepcidin antimicrobial peptide		Hemochromatosis, type 2B		
ADH1B (*103720)	Alcohol dehydrogenase 1B	rs1229984 A>G rs2066702 C>T	G/C, higher alcohol consumption. A/T, accumulation of acetaldehyde	Reduce the alcohol consumption	
ADH1C (*103730)	Alcohol dehydrogenase 1C	rs1693482 C>T (T) rs698 T>A,C (C)	Type II alcoholism		
ALDH2 (*100650)	Aldehyde dehydrogenase 2 family member	rs671 G>A (A)	Acute alcohol sensitivity (#610251)		
CYP1A2 (+124060)	Cytochrome P450 family 1 subfamily A member 2	rs762551 C>A (C)	Higher risk of nonfatal myocardial infarction	Reduce caffeine consumption	doi: 10.1007/s00213-010-1900-1
ADORA2A (*102776)	Adenosine A2a receptor	rs5751876 T>C (C)	Greater caffeine sensitivity, sleep impairment, increased beta activity during non-REM sleep		
		rs35320474 delT (T)	Greater caffeine-induced anxiety		
DRD2	Dopamine receptor D2	rs1110976 T>G (G)	Greater caffeine-induced anxiety		
COMT	Catechol-O-methyl-transferase	rs4680 G>A (A)	Higher risk of acute myocardial infarction		
ALDOB (*612724)	Fructose-bisphosphate B aldolase	rs1800546 C>G (G) rs76917243 G>T (T) rs118204425 AAGdel (del)	Fructose intolerance (#229600)	Reduce consumption of fruit and vegetables	OMIM
UGT1A1 (*191740)	UDP glucuronosyl-transferase family 1 member A1	rs6742078 G>T (T)	Bilirubin serum level (#601816)	Reduce the consumption of proteins	
G6PD (*305900)	Glucose-6-phosphate dehydrogenase	rs1050829 T>A,C (A) rs1050828 C>T (T)	Nonspherocytic hemolytic anemia (#300908)	Avoid the consumption of broad beans	

Table 3. Genes with their SNPs that influence metabolism of specific nutrients with minor effects on health status

Gene (OMIM ID)	Full name	SNP ID (risk allele)	SNP-associated phenotype	Diet intervention	Reference
BCO1	Beta-carotene oxygenase 1	rs12934922 A>T (T)	Reduced conversion of beta-carotene to retinol	Increase the intake of beta-carotene	SNPedia
		rs7501331 C>T (T)			
GC	GC Vitamin D Binding Protein	rs2282679 T>G (G)	Lower vitamin D levels	Increase consumpion of vitamin D-containing food	
		rs4588 G>T (T)			
		rs842999 C>G (C)			
SLC23A1	Solute carrier family 23 member 1	rs33972313 C>T (T)	Reduction of circulating levels of vitamin C	Increase consumpion of vitamin C-containing food	doi:10.3945/ajcn.2010.29438
SLC30A8	Solute carrier family 30 member 8	rs11558471 A>G (G)	Susceptibility to diabetes mellitus	Reduce consumption of food with high content of carbohydrates	doi:10.1186/1471-2350-11-97
SLC5A6	Solute carrier family 5 member 6	rs1395 G>A (A)	Reduced intestinal uptake, cellular delivery and transplacental transport of pantothenate and biotin	Increase consumption of biotin- and pantothenate-containing food	doi:10.1111/jnc.13092
TCN2	Transcobalamin 2	rs1801198 C>G (G)	Decreased serum vitamin B12, increased homocysteine	Increase consumption of B12-containing food	SNPedia
TTPA	Alpha tocopherol transfer protein	rs4501570 G>A (A)	Vitamin E deficiency	Increase consumption of vitam E-containing food	doi:10.3945/jn.112.160333
		rs4587328 T>C (C)			
		rs4606052 C>T (T)			
VDR	Vitamin D receptor	rs731236 A>G (G)	Immune weakness, increased cancer risk, early bone loss, increased cognitive decline risk, mood disorders	Increase consumption of vitam D-containing food	SNPedia
CYP2R1	Cytochrome P450 family 2 subfamily R member 1	rs10741657 A>G (G)	Lower vitamin D levels	Increase consumption of food rich in vitamin D	OMIM
		rs10766197 A>G (A)			
LPA	Lipoprotein(A)	rs10455872 A>G (G) rs3798220 C>T (C)	Coronary artery disease	Reduce trygliceride and cholesterol consumption	SNPedia
			Cardiovascular events risk		
CDKN2B-AS1	Cyclin dependent kinase inhibitor 2B-antisense RNA 1	rs10757274 A>G (G) rs2383206 A>G (G) rs2383207 A>G (G)	Heart attack risk		
Intergenic	/	rs10757278 A>G (G)	Heart disease risk		

(continued on next page)

Table 3 *(continued)***.** Genes with their SNPs that influence metabolism of specific nutrients with minor effects on health status

Gene (OMIM ID)	Full name	SNP ID (risk allele)	SNP-associated phenotype	Diet intervention	Reference
MC4R	Melanocortin 4 receptor	rs17782313 C>T (C)	Increased BMI	Reduce calorie intake	SNPedia
APOA2	Apolipoprotein A2	rs5082 C>T (C)	Higher total energy, fat, protein intake		
PCSK1	Proprotein convertase subtilisin/Kexin type 1	rs6232 A>G (G)	Obesity and insulin sensitivity higher risk		
APOA5	Apolipoprotein A5	rs662799 A>G (G)	Early heart attack higher risk; less weight gain on high fat diets		
SH2B1	SH2B adaptor protein 1	rs7498665 A>G (G)	Obesity; type-2 diabetes		
SLC2A2	Solute carrier family 2 member 2	rs5400 C>T (T)	Higher sugar consumption		
F2	Coagulation factor II, thrombin	rs1799963 A>G (A)	Thrombosis and cerebral stroke higher risk	Reduce tryglicerides and cholesterol consumption	
F5	Coagulation factor V	rs6025 A>G (A)	Thrombosis higher risk		
FUT2	Fucosyltransferase 2	rs602662 A>G (G)	Lower vitamin B12 levels	Increase consumption of food rich in vitamin B12	
ALPL	Biomineralization associated alkaline phosphatase	rs4654748 C>T (C)	Lower Vitamin B6 blood concentration	Increase consumption of food rich in vitamin B6	
CYP2R1	Cytochrome P450 family 2 subfamily R member 1	rs10741657 A>G (G) rs10766197 A>G (A)	Lower vitamin D levels	Increase consumption of food rich in vitamin D, increase sun exposure	
GC	GC vitamin D binding protein	rs4588 G>T (T) rs842999 C>G (C)			
MTHFR (*607093)	Methylenetetrahydrofolate reductase	rs1801133 G>A (A)	Homocystinuria (#236250)	Increase folic acid intake	OMIM
CBS (*613381)	Cystathionine beta synthase	rs121964962 C>T (T)	Homocystinuria (#236200)		
FOXO3	Forkhead box O3	rs2802292 C>T (T) rs2802288 A>G (A) rs2802292 T>G (G)	Longer lifespan		SNPedia
SIRT1	Sirtuin 1	rs3740051 rs2236319 rs2272773	Higher basal energy expenditure		doi:10.1371/journal.pone.0058636
PEMT	Phosphatidylethanolamine N-methyltransferase	rs12325817 G>C (C)	Low choline	Increase choline intake	doi:10.1096/fj.06-5734com
CHDH	Choline dehydrogenase	rs12676 G>T (T)			

Many of these tests aim at informing the susceptibility to different diseases while some deliver nutrition recommendations (1). As a result, supporters of this technology assert that the information provided by these tests may result in a positive impact on health behaviors such as diet, smoking and exercise thus preventing the development of chronic diseases. However, unregulated nature of the industry is a continuous source of controversies surrounding DTC genetic testing.

The major requirement of a nutrigenetic test is that the outcomes must specify a diet-related recommendation that is advantageous for individuals. In addition to that, the results should be based on evidences that have been replicated and give consistent results. Inferences should be drawn based on realistic approaches. Ethical issues should be addressed accordingly.

Ethical concerns related to commercial genetic testing

Keeping in view the quality of genetic profiling tests and their consequent impacts on human life, these tests are prone to several ethical issues related to human welfare, sensitivity of such information and psychological effects of test outcomes. Nearly two million genetic test panels are commercially available with different companies analyzing different genetic polymorphisms (158,159).

Dietary recommendations based on genetic tests that give inconclusive or unreliable information may result in unwarranted limitations and issues (160).

In addition, the interpretation of these results is very important. Only a highly trained health professional having an in-depth knowledge of gene-diet-environment interactions should actually be allowed to interpret the results and extend recommendations . This implicates the need of education in the nutrigenetic, nutrigenomic and nutri-epigenomic disciplines and such courses should be included in curriculum (161).

Guidelines and legal regulations for genetic testing and personalised nutrition

The main aim for the guidelines and regulation for genetic test is to protect individuals from the services that can harm the individual physically, sentimentally or psychologically and to safeguard their rights. For genetic testing and personalized nutrition the regulations are mostly pertaining to analytical methods, clinical validity and clinical utility of the results. Due to increased trend of nutrigenetic research and its practical applications in commercial perspective several public, private organizations have developed guidelines for ensuring safety and well-being of human subjects that are either involved in the studies or are consumers of DTC and dietary prescriptions. European nutrigenomics organization (NuGO) established guidelines for the nutrition genomic research in 2007 (162). These guidelines were formulated based on the international laws safeguarding basic human rights. These specifically mention the importance of informed consent for participation of human subjects in any of the nutrigenetics or nutrigenomic trials or observation studies. However these guidelines are not law so every research involving human subjects should abide by the local legislations of that area. NuGO has highlighted the ethical issue related to genetic testing and consequent release of results for any studies related to nutrigenomics. According to the guidelines all possible measures should be taken in disclosing the results of genetic testing to individuals. For instance it is stated that: *'Genotype results attained during nutrigenomics research should preferably be communicated to the research volunteers on a study group level, and should not be disclosed individually'*. The reason being scarce scientific evidence linking specific genetic variant to diet sensitive pathological condition or response to any dietary intervention. Besides that phenotypic expression of a particular genotype is influenced by many confounding factors hence it is very difficult to be interpreted with respect to health risks and benefits for a particular individual. Moreover disclosing the results of epidemiological studies with large number of subjects could possibly convert the studies into mass screening which may give rise to different budgeting and counselling implications (162). In case of test result disclosure to individuals NuGO advices to convey the results through highly trained professionals who can answer any questions related to outcome of results and detailed written results should also be given in case the consultation by Physician or health care provider is required.

In addition to organizations like NuGO, the government organizations and the agencies of various countries have published rules regulating DTC tests which help to explain, inform and aware individuals. In USA there are three agencies regulating the genetic tests: FDA (Food and Drug Administration), CMS (Centers for medical and Medicaid services), FTC (Federal trade commission) (163). Furthermore, EU also issued a paper in 2002 based on the guidelines of genetic tests that addresses patients' privileges in several European countries, mainly concerning to the right to acquire information, confidentiality, privacy and informed consent (164). The human genetics commission (HGC) in UK published a paper in 2010 on ethical guidelines for the genetic tests including the transparency, availability, ease of getting information and standardized testing procedures (165). Similarly the German governments implemented instructions associated to the authorization of laboratories, the necessity for well-versed agreement and genetic counselling (166). While there are no particular regulation for DTC tests in Belgium and Netherland yet there is a law stating that compelling the involvement of medical physician DTC tests of a medical nature in Belgium (167) and obtaining a permit from the Dutch Minister of welfare and sports in the Netherlands for some genetic tests (168). Whereas the department of health of the Australian government decreed that that testing should guarantee safety and quality and forbids the sale of DTC tests for severe diseases However the regulatory framework in Europe, Food4Me however concluded that neither EU nor its associate states have legal instruments specially dealing with personalized nutrition (169,170).

Controversies related to commercial genetic testing and personalised nutrition

Several controversies are in the air because of rapid increase in genetic testing services aimed at providing tailor made fancy diets and specifically because of some of web based companies and their fraudulent claims. Besides a research boom in the field of nutrigenetic the authenticity of genetic basis of DTCs and the dietary recommendations are still debatable. This is particularly due to the reason that where majority of nutrigenomic studies are thriving to find an evidence of association of genetic variants, polymorphisms and mutations with dietary/ metabolic phenotypes, a considerable amount of observational studies and trials based on large cohorts of human subjects have proven no association. Notable examples in this regard are the 'PREDICT' study involving 700 twins and 400 non twins. Their preliminary results presented at the 2019 meeting of the American Society of Nutrition, confirmed that Different people respond very differently to the same dietary inputs and there is no one dietary approach that's works best for everyone (171). The differences in dietary responses in this study were attributed more to factors such as sleep habits, exercise, stress and gut microbes than to genetics. Another important study DIETFIT concluded that there were no significant differences in weight loss pattern among subjects undertaking diets matched vs unmatched with their genotypes. Moreover there was gene-diet interactions for waist circumference, BMI and body fat percentage (172). Besides these social aspects of personalised nutrition related to an increased healthism and medicalisation of diet are also continuous source of controversy (173).

Conclusion

The advancement in science and availability of technologies like, genomics, transcriptomics, proteomics, metabolomics coupled with information derived from 'The Human Genome Project' has opened the doors for personalised interventions in diet to address metabolic issues related to diseases, disorders and behavioral patterns. Although genes have been found culprit in epidemics like obesity and sedentation, social, moral, psychological and other confounding environmental and epigenetic factors may favor or oppose a typical dietary response. Physical activity holds promise in this regard and adding moderate physical activity to daily life routines coupled with a balanced diet help achieve a desired weight loss goal. Despite of the challenges faced by the nutrigenomics and personalized nutrition in terms of scarcity of scientific evidence, technological barriers, confidentiality and va-

lidity of genetic testing, and ethical concerns related to humans both at nutrigenetic services provision and receiving end, this fields holds promise in improving the quality of human life by interventions complementing, silencing or enhancing the expression of our genes.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Ferguson LR, De Caterina R, Görman U, et al. Guide and position of the international society of nutrigenetics/nutrigenomics on personalised nutrition: part 1 - Fields of precision nutrition. J Nutrigenet Nutrigenomics 2016; 9: 12-27.
2. Kohlmeier M, De Caterina R, Ferguson LR, et al. Guide and position of the international society of nutrigenetics/nutrigenomics on personalized nutrition: part 2 - Ethics, challenges and endeavors of precision nutrition. J Nutrigenet Nutrigenomics 2016; 9: 28-46.
3. Simopoulos AP. Nutrigenetics/nutrigenomics. Annu Rev Public Health 2010; 31: 53–68.
4. Corella D, Ordovas JM. Nutrigenomics in cardiovascular medicine. Circ Cardiovasc Genet 2009; 2: 637–51.
5. Trujillo E, Davis C, Milner J. Nutrigenomics, proteomics, metabolomics, and the practice of dietetics. J Am Diet Assoc 2006; 106: 403–13.
6. Ferguson LR. Nutrigenomics approaches to functional foods. J Am Diet Assoc 2009; 109: 452–8.
7. Kaput J. Nutrigenomics research for personalized nutrition and medicine. Curr Opin Biotechnol 2008; 19: 110–20.
8. Ordovas JM, Corella D. Nutritional genomics. Annu Rev Genomics Hum Genet 2004; 5: 71–118.
9. Fenech MF. Nutriomes and nutrient arrays – the key to personalised nutrition for DNA damage prevention and cancer growth control. Genome Integr 2010; 1: 11.
10. Simopoulos AP, Ordovas JM. World Review of Nutrition and Dietetics. In: Nutrigenetics and Nutrigenomics, Karger, Basel, 2004.
11. Frazer KA, Murray SS, Schork NJ, Topol EJ. Human genetic variation and its contribution to complex traits. Nat Rev Genet 2009; 10: 241–51.
12. Ordovas JM. Gender, a significant factor in the cross talk between genes, environment, and health. Gend Med 2007; 4: S111–22.
13. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet 2007; 8: 253–62.
14. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis 2010; 31: 27–36.
15. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889–94.
16. Farooqi IS, O'Rahilly S. Genetics of obesity in humans. Endocr Rev 2006; 10: 710–8.
17. Martinez JA, Parra MD, Santos JL, Moreno-Aliaga MJ, Marti A, Martinez-Gonzalez MA. Genotype-dependent response to energy-restricted diets in obese subjects: towards personalized nutrition. Asia Pacific J Clin Nutr 2008; 17: 119–22.
18. Razquin C, Marti A, Martinez JA. Evidences on three relevant obesogenes: MC4R, FTO and PPARgamma. Approaches for personalized nutrition. Mol Nutr Food Res 2011; 55: 136–49.
19. Wang J, Wang LJ, Zhong Y, et al. CETP gene polymorphisms and risk of coronary atherosclerosis in a Chinese population. Lipids Health Disease 2013; 12: 176.
20. Lu Y, Tayebi N, Li H, Saha N, Yang H, Heng CK. Association of CETP Taq1B and -629C > A polymorphisms with coronary artery disease and lipid levels in the multi-ethnic Singaporean population. Lipids Health Disease 2013; 12: 85.
21. Huang D, Xie X, Ma YT, Huang Y, Ma X. Endothelial lipase-384A/C polymorphism is associated with acute coronary syndrome and lipid status in elderly Uygur patients in Xinjiang. Genet Testing Mol Biomarkers 2014; 18: 781–4.
22. Knoblauch H, Bauerfeind A, Krahenbuhl C, et al. Common haplotypes in five genes influence genetic variance of LDL and HDL cholesterol in the general population. Hum Mol Genet 2002; 11: 1477–85.
23. Lyssenko V, Lupi R, Marchetti P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest 2007; 117: 2155–63.
24. Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care 2011; 14: 28–34.
25. Mirabello L, Huang WY, Wong JY, et al. The association between leukocyte telomere length and cigarette smoking, dietary and physical variables, and risk of prostate cancer. Aging Cell 2009; 8: 405–13.
26. Liew SC, Gupta ED. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. Eur J Med Genet 2015; 58: 1–10.
27. Cornelis MC, El-Sohemy A, Kabagambe EK, et al. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA 2006; 295: 1135-41.
28. Corella D, Peloso G, Arnett DK, et al. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. Arch Intern Med 2009; 169: 1897-906.
29. Corella D, Tai ES, Sorlí JV, et al. Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene-saturated fat interaction. Int J Obes (Lond) 2011; 35: 666-75.
30. Cahill LE, Fontaine-Bisson B, El-Sohemy A. Functional genetic variants of glutathione S-transferase protect against serum ascorbic acid deficiency. Am J Clin Nutr 2009; 90: 1411-7.
31. Slater NA, Rager ML, Havrda DE, et al. Genetic variation

in CYP2R1 and GC genes associated with vitamin D deficiency status. J Pharm Pract 2017; 30: 31-6.
32. Tanwar VS, Chand MP, Kumar J, et al. Common variant in FUT2 gene is associated with levels of vitamin B(12) in Indian population. Gene 2013; 515: 224-8.
33. Benyamin B, Ferreira MA, Willemsen G, et al. Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. Nat Genet 2009; 41: 1173-5.
34. Nielsen DE, El-Sohemy A. A randomized trial of genetic information for personalized nutrition. Genes Nutr 2012; 7: 559-66.
35. Nielsen DE, El-Sohemy A. Disclosure of genetic information and change in dietary intake: a randomized controlled trial. PLoS One 2014; 9: e112665.
36. De Toro-Martin J, Arsenault BJ, Despres JP, Vohl MC. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. Nutrients 2017; 9: 913.
37. Nizel AE. Personalized nutrition counseling. ASDC J Dent Child 1972; 39: 353–60.
38. Brug J, Campbell M, van Assema P. The application and impact of computer-generated personalized nutrition education: A review of the literature. Patient Educ Couns 1999; 36: 145–56.
39. Stewart-Knox B, Kuznesof S, Robinson J, et al. Factors influencing European consumer uptake of personalised nutrition. Results of a qualitative analysis. Appetite 2013; 66: 67–74.
40. Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. Lancet Diabetes Endocrinol 2018; 6: 416–26.
41. Van Ommen B, van den Broek T, de Hoogh I, et al. Systems biology of personalized nutrition. Nutr Rev 2017; 75: 579–99.
42. Grimaldi KA, van Ommen B, Ordovas JM, et al. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. Genes Nutr 2017; 12: 35.
43. Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. J Inherit Metab Dis 2010; 33: 105–12.
44. de Baulny HO, Abadie V, Feillet F, de Parscau L. Management of phenylketonuria and hyperphenylalaninemia. J Nutr 2007; 137: 1561S–3S.
45. Novelli G, Reichardt JK. Molecular basis of disorders of human galactose metabolism: past, present, and future. Mol Genet Metab 2000; 71: 62–5.
46. Heap GA, van Heel DA. Genetics and pathogenesis of coeliac disease. Semin Immunol 2009; 21: 346–54.
47. Lactose intolerance: your guide to understanding genetic conditions. Available at: https://ghr.nlm.nih.gov/condition/lactose-intolerance. Accessed 05 June 2017.
48. Fallaize R, Macready AL, Butler LT, Ellis JA, Lovegrove JA. An insight into the public acceptance of nutrigenomic-based personalised nutrition. Nutr Res Rev 2013; 26: 39–48.
49. Atkinson SA. Defining the process of dietary reference intakes: frameworkfor the United States and Canada. Am J Clin Nutr 2011; 94: 655S–7S.
50. Taylor C L. Framework for DRI development: components 'known' andcomponents 'to be explored.' 2008, Available at: https://www.nal.usda.gov/sites/default/files/fnic_uploads/Framework_DRI_Development.
51. Timotijevic L, Brown KA, Lähteenmäki L, et al. EURRECA—a framework for considering evidence in public health nutrition policy development. Crit Rev Food Sci Nutr 2013; 53: 1124–34.
52. Claessens M, Contor L, Dhonukshe-Rutten R, et al. EURRECA—principles and future for deriving micronutrient recommendations. Crit Rev Food Sci Nutr 2013; 53: 1135–46.
53. Hruby A, Manson JE, Qi L, et al. Determinants and consequences of obesity. Am J Public Health 2016; 106: 1656–62.
54. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012; 367: 1387–96.
55. Brunkwall L, Chen Y, Hindy G, et al. Sugar-sweetened beverage consumption and genetic predisposition to obesity in 2 Swedish cohorts. Am J Clin Nutr 2016; 104: 809–15.
56. Olsen NJ, Angquist L, Larsen SC, et al. Interactions between genetic variants associated with adiposity traits and soft drinks in relation to longitudinal changes in body weight and waist circumference. Am J Clin Nutr 2016; 104: 816–26.
57. Qi Q, Chu AY, Kang JH, et al. Fried food consumption, genetic risk, and body mass index: Gene-Diet interaction analysis in three us cohort studies. BMJ 2014; 348: g1610.
58. Ahmad S, Rukh G, Varga TV, et al. Gene × physical activity interactions in obesity: Combined analysis of 111,421 individuals of european ancestry. PLoS Genet 2013; 9: e1003607.
59. Tyrrell J, Wood AR, Ames RM, et al. Gene-obesogenic environment interactions in the UK biobank study. Int J Epidemiol 2017; 46: 559-75.
60. Alfredo Martínez J. Perspectives on personalized nutrition for obesity. J Nutrigenet Nutrigenomics 2014; 7: I–III.
61. Marreiro Ddo N, de Sousa AF, Nogueira Ndo N, Oliveira FE. Effect of zinc supplementation on thyroid hormone metabolism of adolescents with Down syndrome. Biol Trace Elem Res 2009; 129: 20–7.
62. Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ. Homocysteine metabolism in children with Down syndrome: in vitro modulation. Am J Hum Genet 2001; 69: 88–95.
63. Ordovas JM, Mooser V: Nutrigenomics and nutrigenetics. Curr Opin Lipidol 2004; 15: 101–8.
64. Rao AD, Sun B, Saxena A, et al. Polymorphisms in the serum- and glucocorticoid-inducible kinase 1 gene are associated with blood pressure and renin response to dietary salt intake. J Hum Hypertens 2013; 27: 176–80.
65. Mustalahti K, Catassi C, Reunanen A, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med 2010; 42: 587–95.

66. Fenech M, El-Sohemy A, Cahill L, et al: Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics 2011; 4: 69–89.
67. Burkhardt R, Kirsten H, Beutner F, et al. Integration of genome-wide SNP data and gene-expression profiles reveals six novel loci and regulatory mechanisms for amino acids and acylcarnitines in whole blood. PLoS Genet 2015; 11: e1005510.
68. Goni L, Cuervo M, Milagro FI, Martínez A. Future perspectives of personalized weight loss interventions based on nutrigenetic, epigenetic, and metagenomic data. J Nutr 2015; 146: 905S–12S.
69. Precone V, Beccari T, Stuppia L, et al. Taste, olfactory and texture related genes and food choices: Implications on health status. Eur Rev Med Pharmacol Sci 2019; 23: 1305–21.
70. Grimaldi K. Nutrigenetics and personalized nutrition: Are we ready for DNA-based dietary advice? Pers Med 2014; 11: 297–307.
71. De Caterina R, El-Sohemy A. Moving towards specific nutrigenetic recommendation algorithms: caffeine, genetic variation and cardiovascular risk. J Nutr Nutr 2016; 9: 106–15.
72. Frayling TM, Timpson NJ, Weedon M, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889–94.
73. Hetherington MM, Cecil JE. Gene-environment interactions in obesity. Forum Nutr 2009; 63: 195–203.
74. Ortega-Azorín C, Sorlí JV, Asensio EM, et al. Associations of the FTO rs9939609 and the MC4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the Mediterranean diet pattern is low. Cardiovasc Diabetol 2012; 11: 137.
75. Fisher E, Boeing H, Fritsche A, Doering F, Joost HG, Schulze MB. Whole-grain consumption and transcription factor-7-like 2 (TCF7L2) rs7903146: Gene–diet interaction in modulating type 2 diabetes risk. Br J Nutr 2008; 101: 478–81.
76. Hindy G, Sonestedt E, Ericson U, et al. Role of TCF7L2 risk variant and dietary fibre intake on incident type 2 diabetes. Diabetologia 2012; 55: 2646–54.
77. Wirström T, Hilding A, Gu HF, Ostenson CG, Björklund A. Consumption of whole grain reduces risk of deteriorating glucose tolerance, including progression to prediabetes. Am J Clin Nutr 2012; 97: 179–87.
78. López-Ortiz MM, Garay-Sevilla ME, Tejero ME, Pérez-Luque E. Analysis of the interaction between transcription factor 7-like 2 genetic variants with nopal and wholegrain fibre intake: Effects on anthropometric and metabolic characteristics in type 2 diabetes patients. Br J Nutr 2016; 116: 969–78.
79. Franzago M, Fraticelli F, Nicolucci A, et al. Molecular analysis of a genetic variants panel related to nutrients and metabolism: association with susceptibility to gestational diabetes and cardiometabolic risk in affected women. J Diabetes Res 2017; 2017: 4612623.
80. Franzago M, Fraticelli F, Marchetti D, et al. Nutrigenetic variants and cardio-metabolic risk in women with or without gestational diabetes. Diabetes Res Clin Pract 2018; 137: 64–71.
81. Franzago M, Fraticelli F, Di Nicola M, et al. Early subclinical atherosclerosis in gestational diabetes: the predictive role of routine biomarkers and nutrigenetic variants. J Diabetes Res 2018; 2018: 9242579.
82. Dhurandhar NV, Schoeller D, Brown AW, et al. Energy balance measurement: When something is not better than nothing. Int J Obes 2014; 39: 1109–13.
83. Archer E, Marlow ML, Lavie CJ. Controversy and debate: memory based methods paper 3: nutrition's 'Black Swans': Our reply. J Clin Epidemiol 2018; 104: 130–5.
84. Matsuo T, Nakata Y, Murotake Y, Hotta K, Tanaka K. Effects of FTO genotype on weight loss and metabolic risk factors in response to calorie restriction among Japanese women. Obesity (Silver Spring) 2012; 20: 1122–6.
85. Zheng Y, Huang T, Zhang X, et al. Dietary fat modifies the effects of FTO genotype on changes in insulin sensitivity. J Nutr 2015; 145: 977–82.
86. Grau K, Hansen T, Holst C, et al. Macronutrient-specific effect of FTO rs9939609 in response to a 10-week randomized hypo-energetic diet among obese Europeans. Int J Obes (Lond) 2009; 33: 1227–34.
87. Zhang X, Qi Q, Zhang C, et al. 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: 3005–11.
88. Mitchell JA, Church TS, Rankinen T, Earnest CP, Sui X, Blair SN. FTO genotype and the weight loss benefits of moderate intensity exercise. Obesity (Silver Spring) 2010; 18: 641–3.
89. Labayen I, Margareto J, Maldonado-Martin S, et al. Independent and combined influence of the FTO rs9939609 and MC4Rrs17782313 polymorphisms on hypocaloric diet induced changes in body mass and composition and energy metabolism in non-morbid obese premenopausal women. Nutr Hosp 2015; 31: 2025–32.
90. De Luis DA, Izaola O, Primo D, et al. Role of rs1501299 variant in the adiponectin gene on total adiponectin levels, insulin resistance and weight loss after a Mediterranean hypocaloric diet. Diabetes Res Clin Pract 2019; 148: 262–7.
91. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425–32.
92. De Luis Roman D, de la Fuente RA, Sagrado MG, Izaola O, Vicente RC. Leptin receptor Lys656Asn polymorphism is associated with decreased leptin response and weight loss secondary to a lifestyle modification in obese patients. Arch Med Res 2006; 37: 854–9.
93. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. Nat Rev Genet 2009; 10: 431-42.

94. Choquet H, Meyre D. Genetics of obesity: What have we learned? Curr Genomics 2011; 12: 169-79.
95. Labayen I, Margareto J, Maldonado-Martin S, et al. Independent and combined influence of the FTO rs9939609 and MC4R rs17782313 polymorphisms on hypocaloric diet induced changes in body mass and composition and energy metabolism in non-morbid obese premenopausal women. Nutr Hosp 2015; 31: 2025–32.
96. Pan Q, Delahanty LM, Jablonski KA, et al. Variation at the melanocortin 4 receptor gene and response to weight-loss interventions in the diabetes prevention program. Obesity (Silver Spring) 2013; 21: E520–6.
97. Huang T, Huang J, Qi Q, et al. PCSK7genotype modifies effect of a weight-loss diet on 2-year changes of insulin resistance: The pounds lost trial. Diabetes Care 2015; 38: 439–44.
98. Tonjes A, Scholz M, Loeffler M, Stumvoll M. Association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma with pre-diabetic phenotypes: meta-analysis of 57 studies on nondiabetic individuals. Diabetes Care 2006; 29: 2489-97.
99. Meirhaeghe A, Amouyel P. Impact of genetic variation of PPAR gamma in humans. Mol Genet Metab 2004; 83: 93-102.
100. Ruiz JR, Larrarte E, Margareto J, Ares R, Labayen I. Role of β_2-adrenergic receptor polymorphisms on body weight and body composition response to energy restriction in obese women: preliminary results. Obesity (Silver Spring) 2011; 19: 212–5.
101. Saliba LF, Reis RS, Brownson RC, et al. Obesity-related gene ADRB2, ADRB3 and GHRL polymorphisms and the response to a weight loss diet intervention in adult women. Genet Mol Biol 2014; 37: 15–22.
102. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat vs low-carbohydrate diet on 12-Month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA 2018; 319: 667–79.
103. Tahara A, Osaki Y, Kishimoto T. Effect of the β3-adrenergic receptor gene polymorphism Trp64Arg on BMI reduction associated with an exercise-based intervention program in Japanese middle-aged males. Environ Health Prev Med 2010; 15: 392–7.
104. Shiwaku K, Nogi A, Anuurad E, et al. Difficulty in losing weight by behavioral intervention for women with Trp64Arg polymorphism of the beta3-adrenergic receptor gene. Int J Obes Relat Metab Disord 2003; 27: 1028–36.
105. Korbonits M, Gueorguiev M, O'Grady E, et al. A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. J Clin Endocrinol Metab 2002; 87: 4005-8.
106. Zarebska A, Jastrzebski Z, Cieszczyk P, et al. The Pro12Ala polymorphism of the peroxisome proliferator-activated receptor gamma gene modifies the association of physical activity and body mass changes in Polish women. PPAR Res 2014; 2014: 373782.
107. Mocking RJT, Lok A, Assies J, et al. Ala54Thr fatty acid-binding protein 2 (FABP2) polymorphism in recurrent depression: associations with fatty acid concentrations and waist circumference. PLoS One 2012; 8: e82980.
108. 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: 917–22.
109. Suchanek P, Lorenzova A, Poledne R, Hubacek JA. Changes of plasma lipids during weight reduction in females depends on APOA5 variants. Ann Nutr Metab 2008; 53: 104–8.
110. De Luis DA, Izaola O, Primo D, Aller R. Role of rs670 variant of APOA1 gene on lipid profile, insulin resistance and adipokine levels in obese subjects after weight loss with a dietary intervention. Diabetes Res Clin Pract 2018; 142: 139–45.
111. Xu M, Ng SS, Bray GA, et al. Dietary fat intake modifies the effect of a common variant in the LIPC gene on changes in serum lipid concentrations during a long-term weight-loss intervention trial. J Nutr 2015; 145: 1289–94.
112. Qi Q, Durst R, Schwarzfuchs D, et al. 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: 713–21.
113. De Luis DA, Izaola O, Primo D, Aller R. Association of the rs10830963 polymorphism in melatonin receptor type 1B (MTNR1B) with metabolic response after weight loss secondary to a hypocaloric diet based in Mediterranean style. Clin Nutr 2018; 37: 1563–8.
114. Goni L, Sun D, Heianza Y, et al. Macronutrient-specific effect of the MTNR1B genotype on lipid levels in response to 2 year weight-loss diets. J Lipid Res 2018; 59: 155–61.
115. Lin X, Qi Q, Zheng Y, et al. Neuropeptide Y genotype, central obesity, and abdominal fat distribution: the POUNDS LOST trial. Am J Clin Nutr 2015; 102: 514–9.
116. 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: 506–13.
117. 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: 563–71.
118. Qi Q, Xu M, Wu H, et al. IRS1 genotype modulates metabolic syndrome reversion in response to 2-year weight-loss diet intervention: the POUNDS LOST trial. Diabetes Care 2013; 36: 3442–7.
119. Grau K, Cauchi S, Holst C, et al. TCF7L2 rs7903146macronutrient interaction in obese individuals' responses to a 10-wk randomized hypoenergetic diet. Am J Clin Nutr 2010; 91: 472–9.

120. Löffler D, Behrendt S, Creemers JWM, et al. Functional and clinical relevance of novel and known PCSK1 variants for childhood obesity and glucose metabolism. Mol Metab 2016; 6: 295-305.
121. Huang T, Huang J, Qi Q, et al. PCSK7 genotype modifies effect of a weight-loss diet on 2-year changes of insulin resistance: the POUNDS LOST trial. Diabetes Care 2015; 38: 439–44.
122. Rankinen T, Bouchard C. Gene-physical activity interactions: overview of human studies. Obesity (Silver Spring) 2008; 16: S47-50.
123. Lin X, Eaton CB, Manson JE, Liu S. The genetics of physical activity. Curr Cardiol Rep 2017; 19: 119.
124. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2015; 4: e002014.
125. Goryakin Y, Aldea A, Lerouge A, et al. Promoting sport and physical activity in Italy: a cost-effectiveness analysis of seven innovative public health policies. Ann Ig 2019; 31: 614-25.
126. Carlson SA, Fulton JE, Pratt M, Yang Z, Adams EK. Inadequate physical activity and health care expenditures in the United States. Prog Cardiovasc Dis 2015; 57: 315–23.
127. De Geus EJ, De Moor MH. Genes, exercise, and psychological factors. In: Genetic and molecular aspects of sport performance. Oxford: Blackwell Publishing; 2011.
128. Perusse L, Tremblay A, Leblanc C, Bouchard C. Genetic and environmental influences on level of habitual physical activity and exercise participation. Am J Epidemiol 1989; 129: 1012–22.
129. Simonen RL, Perusse L, Rankinen T, Rice T, Rao DC, Bouchard C. Familial aggregation of physical activity levels in the Quebec Family Study. Med Sci Sports Exerc 2002; 34: 1137–42.
130. Sallis JF, Patterson TL, Buono MJ, Atkins CJ, Nader PR. Aggregation of physical activity habits in Mexican-American and Anglo families. J Behav Med 1988; 11: 31–41.
131. Choh AC, Demerath EW, Lee M, et al. Genetic analysis of self-reported physical activity and adiposity: the Southwest Ohio Family Study. Public Health Nutr 2009; 12: 1052–60.
132. Butte NF, Cai G, Cole SA, Comuzzie AG. Viva la Familia Study: genetic and environmental contributions to childhood obesity and its comorbidities in the Hispanic population. Am J Clin Nutr 2006; 84: 646–54.
133. Moore LL, Lombardi DA, White MJ, Campbell JL, Oliveria SA, RC. Influence of parents' physical activity levels on activity levels of young children. J Pediatr 1991; 118: 215–9.
134. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996; 273: 1516–7.
135. Altmuller J, Palmer LJ, Fischer G, Scherb H, Wjst M. Genome-wide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 2001; 69: 936–50.
136. Simonen RL, Rankinen T, Perusse L, et al. Genome-wide linkage scan for physical activity levels in the Quebec Family Study. Med Sci Sports Exerc 2003; 35: 1355–9.
137. Cai G, Cole SA, Butte N, et al. A quantitative trait locus on chromosome 18q for physical activity and dietary intake in Hispanic children. Obesity (Silver Spring) 2006; 14: 1596–604.
138. De Moor MH, Posthuma D, Hottenga JJ, Willemsen G, Boomsma DI, De Geus EJ. Genome-wide linkage scan for exercise participation in Dutch sibling pairs. Eur J Hum Genet 2007; 15: 1252–9.
139. Stefan N, Vozarova B, Del Parigi A, et al. The Gln223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. Int J Obes Relat Metab Disord 2002; 26: 1629–32.
140. Richert L, Chevalley T, Manen D, Bonjour JP, Rizzoli R, Ferrari S. Bone mass in prepubertal boys is associated with a Gln223Arg amino acid substitution in the leptin receptor. J Clin Endocrinol Metab 2007; 92: 4380–6.
141. De Moor MH, Liu YJ, Boomsma DI, et al. Genome-wide association study of exercise behavior in Dutch and American adults. Med Sci Sports Exerc 2009; 41: 1887–95.
142. Voisin S, Eynon N, Yan X, Bishop DJ. Exercise training and DNA methylation in humans. Acta Physiol (Oxf) 2015; 213: 39–59.
143. Krieger JW, Sitren HS, Daniels MJ, Langkamp-Henken B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression Am J Clin Nutr 2006; 83: 260–74.
144. Knapik JJ. The importance of physical fitness for injury prevention: part 2. J Spec Oper Med 2015; 15: 112–5.
145. Van Deveire KN, Scranton SK, Kostek MA, et al. Variants of the ankyrin repeat domain 6 gene (ANKRD6) and muscle and physical activity phenotypes among European-derived American adults. J Strength Cond Res 2012; 26: 1740-8.
146. Bruneau M Jr, Walsh S, Selinsky E, et al. A genetic variant in IL-15Ra correlates with physical activity among European-American adults. Mol Genet Genomic Med 2018; 6: 401–8.
147. Gielen M, Westerterp-Plantenga MS, Bouwman FG, et al. Heritability and genetic etiology of habitual physical activity: a twin study with objective measures. Genes Nutr 2014; 9: 415.
148. Akhmetov II, Astranenkova IV, Rogozkin VA. Mol Biol (Mosk) 2007; 41: 852-7.
149. Stefan N, Vozarova B, Del Parigi A, et al. The Gln223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. Int J Obes Relat Metab Disord 2002; 26: 1629–32.
150. De Moor MH, Posthuma D, Hottenga JJ, Willemsen G, Boomsma DI, De Geus EJ. Genome-wide linkage scan for exercise participation in Dutch sibling pairs. Eur J Hum Genet 2007; 15: 1252–9.

151. Lorentzon M, Lorentzon R, Lerner UH, Nordstrom P. Calcium sensing receptor gene polymorphism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. Eur J Endocrinol 2001; 144: 257–61.
152. Winnicki M, Accurso V, Hoffmann M, et al. Physical activity and angiotensin-converting enzyme gene polymorphism in mild hypertensives. Am J Med Genet A 2004; 125A: 38–44.
153. Loos RJ, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008; 40: 768–75.
154. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med 2011; 8: e1001116.
155. Rankinen T, Rice T, Teran-Garcia M, Rao DC, Bouchard C. FTO genotype is associated with exercise training-induced changes in body composition. Obesity 2010; 18: 322–6.
156. Cassidy S, Chau JY, Catt M, et al. Cross-sectional study of diet, physical activity, television viewing and sleep duration in 233 110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and type 2 diabetes. BMJ Open 2016; 6: e010038.
157. Franks PW, Jablonski KA, Delahanty LM, et al. Assessing gene-treatment interactions at the FTO and INSIG2 loci on obesity-related traits in the Diabetes Prevention Program. Diabetologia 2008; 51: 2214–23.
158. Liaw YC, Liaw YP, Lan TH. Physical activity might reduce the adverse impacts of the FTO gene variant rs3751812 on the body mass index of adults in Taiwan. Genes (Basel) 2019; 10: 354.
159. Bruneau M Jr, Angelopoulos TJ, Gordon P, et al. The angiotensin-converting enzyme insertion/deletion polymorphism rs4340 associates with habitual physical activity among European American adults. Mol Genet Genomic Med 2017; 5: 524-30.
160. Khoury MJ, Gwinn M, Bowen MS, Dotson WD. Beyond base pairs to bedside: a population perspective on how genomics can improve health. Am J Public Health 2012; 102: 34–7.
161. San-Cristobal R, Milagro FI, Martinez JA. Future challenges and present ethical considerations in the use of personalized nutrition based on genetic advice. J Acad Nutr Diet 2013; 113: 1447–54.
162. Bergmann MM, Gorman U, Mathers JC. Bioethical considerations for human nutrigenomics. Annu Rev Nutr 2008; 28: 447–67.
163. Arab L. Individualized nutritional recommendations: do we have the measurements needed to assess risk and make dietary recommendations? Proc Nutr Soc 2004; 63: 167–72.
164. The NuGO Bioethics Guidelines on Human Studies: http://nugo.dife.de/bot/index.php - Oslo, September 17th, 2007.
165. http://www.genome.gov/10002335
166. Human Genetic Commission (UK HGC): A common framework of principles for direct-to-consumer genetic testing services. London, Human Genome Commission, 2010.
167. The German Human Genetic Examination Act (Gesetz über genetische Untersuchungen bei Menschen Gendiagnostikgesetz-GenDG), 2009.
168. Superior Health Council: Publication of the Superior Health Council No. 8714. Brussels, Superior Health-Council, 2012.
169. Borry P, van Hellemondt RE, Sprumont D, et al. Legislation on direct-to consumer genetic testing in seven European countries. Eur J Hum Genet 2012; 20: 715–21.
170. Gibney MJ, Walsh M. Personalised nutrition: an integrated analysis of opportunities and challenges white paper by Food4Me partners. Available at: https://cordis.europa.eu/project/id/265494/reporting/it
171. Berry S, Valdes A, Davies R, et al. Predicting personal metabolic responses to food using multi-omics machine learning in over 1000 twins and singletons from the UK and US: The PREDICT I Study (OR31-01-19). Curr Dev Nutr 2019; 3.
172. Stanton MV, Robinson JL, Kirkpatrick SM, et al. DIET-FITS study (diet intervention examining the factors interacting with treatment success) - Study design and methods. Contemp Clin Trials 2017; 53: 151-61.
173. Gorman U. Ethical issues raised by personalized nutrition based on genetic information. Genes Nutr 2006; 1: 13–22.

Received: 3 September 2020
Accepted: 14 October 2020
Correspondence:
Stefano Paolacci
Via delle Maioliche, 57/D, Rovereto (TN), Italy
E-mail: stefano.paolacci@assomagi.org