ELSEVIER

Journal of Nutritional Biochemistry 14 (2003) 426–451

THE JOURNAL OF Nutritional Biochemistry

Reviews: Current Topics

Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases (Review)

Alexandre Loktionov

MRC Dunn Human Nutrition Unit, Cambridge CB2 2XY, UK

Received 8 November 2002; received in revised form 29 January 2003; accepted 25 February 2003

Abstract

Rapid progress in human genome decoding has accelerated search for the role of gene polymorphisms in the pathogenesis of complex multifactorial diseases. This review summarizes the results of recent studies on the associations of common gene variants with multifactorial chronic conditions strongly affected by nutritional factors. Three main individual sections discuss genes related to energy homeostasis regulation and obesity, cardiovascular disease (CVD), and cancer. It is evident that several major chronic diseases are closely related (often through obesity) to deregulation of energy homeostasis. Multiple polymorphic genes encoding central and peripheral determinants of energy intake and expenditure have been revealed over the past decade. Food intake control may be affected by polymorphisms in the genes encoding taste receptors and a number of peripheral signaling peptides such as insulin, leptin, ghrelin, cholecystokinin, and corresponding receptors. Polymorphic central regulators of energy intake include hypothalamic neuropeptide Y, agouti-related protein, melanocortin pathway factors, CART (cocaine- and amphetamine-regulated transcript), some other neuropeptides, and receptors for these molecules. Potentially important polymorphisms in the genes encoding energy expenditure modulators (alpha- and beta- adrenoceptors, uncoupling proteins, and regulators of adipocyte growth and differentiation) are also discussed. CVD-related gene polymorphisms comprising those involved in the pathogenesis of atherosclerosis, blood pressure regulation, hemostasis control, and homocysteine metabolism are considered in a separate section with emphasis on multiple polymorphisms affecting lipid transport and metabolism and their interactions with diet. Cancer-associated polymorphisms are discussed for groups of genes encoding enzymes of xenobiotic metabolism, DNA repair enzymes, factors involved in the cell cycle control, hormonal regulation-associated proteins, enzymes related to DNA methylation through folate metabolism, and angiogenesis-related factors.

There is an apparent progress in the field with hundreds of new gene polymorphisms discovered and characterized, however firm evidence consistently linking them with pathogenesis of complex chronic diseases is still limited. Ways of improving the efficiency of candidate gene approach-based studies are discussed in a short separate section. Successful unraveling of interaction between dietary factors, polymorphisms, and pathogenesis of several multifactorial diseases is exemplified by studies of folate metabolism in relation to CVD and cancer. It appears that several new directions emerge as targets of research on the role of genetic variation in relation to diet and complex chronic diseases. Regulation of energy homeostasis is a fundamental problem insufficiently investigated in this context so far. Impacts of genetic variation on systems controlling angiogenesis, inflammatory reactions, and cell growth and differentiation (comprising regulation of the cell cycle, DNA repair, and DNA methylation) are also largely unknown and need thorough analysis. These goals can be achieved by complex simultaneous analysis of multiple polymorphic genes controlling carefully defined and selected elements of relevant metabolic and regulatory pathways in meticulously designed large-scale studies.

Keywords: Gene variants; Diet; Obesity; Cardiovascular disease; Cancer

1. Introduction

Recent rapid progress in the human genome sequence determination [1,2] has opened plentiful opportunities for investigating the relationship between numerous polymorphic gene variants present in human populations and their impact in the pathogenesis of various pathologic conditions [3-5]. Indisputable achievements have already been made with the use of genetic linkage and positional cloning methods to discover gene mutations directly causing some relatively rare monogenic (Mendelian) hereditary diseases such as retinoblastoma, cystic fibrosis, familial adenomatous polyposis (FAP) and a number of others [6]. It is, however,

Corresponding author. (A. Loktinov)
E-mail address: asl@mrc-dunn.cam.ac.uk

0955-2863/03/$ – see front matter
doi:10.1016/S0955-2863(03)00032-9

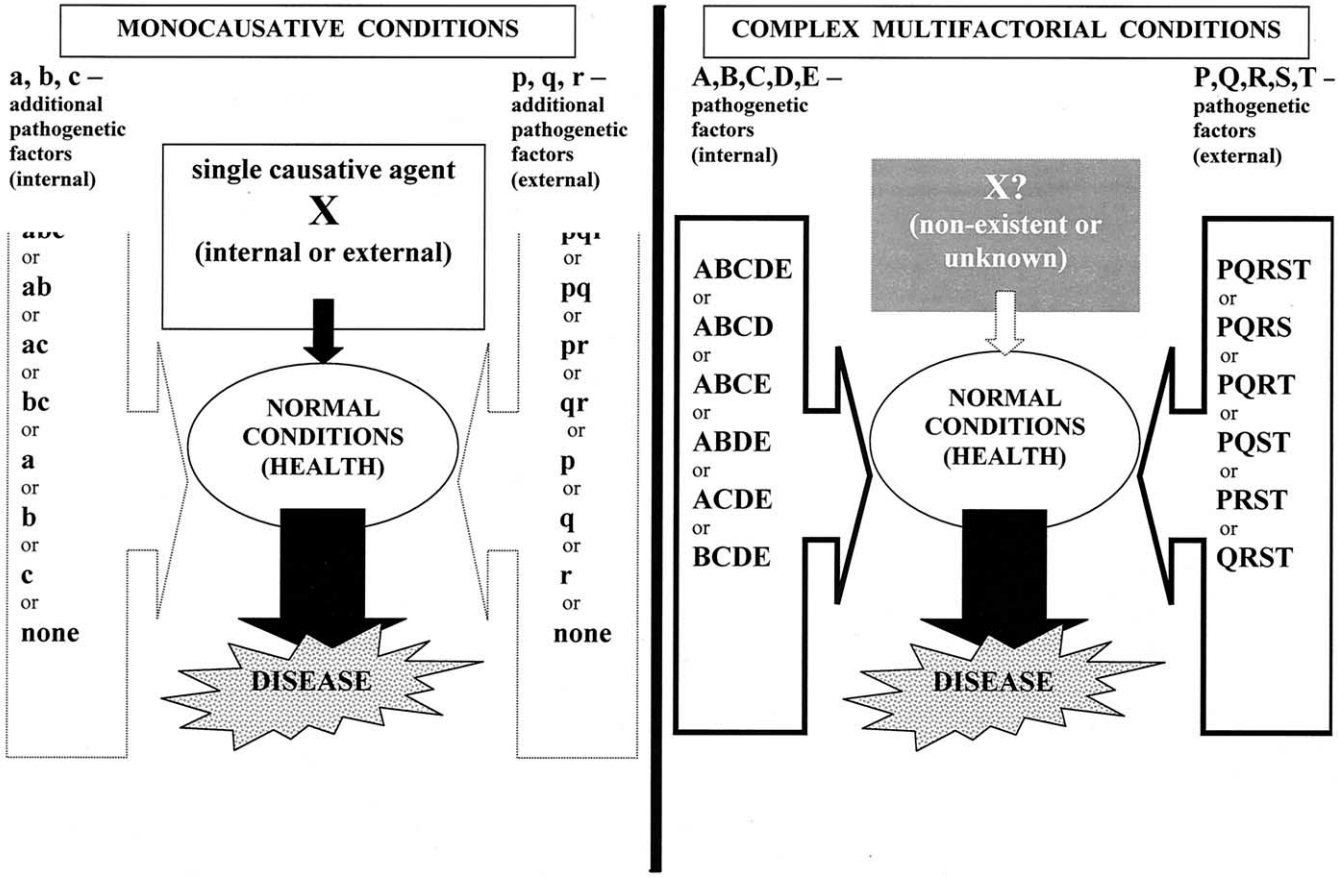

Fig. 1. Schematic comparison of monocausative and complex multifactorial conditions. **Monocausative conditions** always require a single causative agent (**X**) determining ethiology of the disease. Additional pathogenetic factors (**a, b, c... p, q, r...**) can modify pathogenesis and clinical manifestations of the condition in a favorable or unfavorable way, however their role is not obligatory. There is no chance to induce the condition by any combination of additionnal pathogenetic factors in the absence of the main agent. **Complex multifactorial conditions** are believed to result from combined effects of multiple ethiopathogenetic factors (**A, B, C, D, E... P, Q, R, S, T...**) acting simultaneously in different combinations. Presumably the disease can develop only after certain "critical mass" of unfavourable factors/effects (often including failure of protective mechanisms) has accumulated (different pathogenetic patterns involving at least four factors in the scheme). Given our incomplete knowledge of the mechanisms of complex multifactorial diseases, the idea of a possibility of the existence of yet unknown causative agents (**X?**) cannot be completely dismissed.

evident that this approach, really powerful for diseases engendered by a single causative genetic factor, fails when applied to disorders with complex multifactorial pathogenesis involving strong environmental component [4,6].

The distinctive feature of diseases with multifactorial pathogenesis is the absence of a single specific causative agent (eg. infection, toxin or highly penetrant germ-line mutation), elimination of which is able to prevent or stop pathologic process development (Fig. 1). It appears that complex interactions of multiple internal and external factors determine probability of developing multifactorial diseases. Individual genetic background, which can be defined as a unique combination of common variants of thousands of polymorphic genes governing metabolic pathways and regulatory systems at different levels, interacts with numerous environmental influences. Diet occupies a special place among these external influences affecting human health. Being an indispensable everyday factor, it is believed to be among the most important risk modulators for several major diseases with multifactorial pathogenesis. Complexity of these diseases makes it impossible to assess impacts of all possible contributing factors. In terms of investigating genetic components of their pathogenesis it means that some polymorphic genes, products of which are most likely to be involved in the disease development, are selected and analyzed as "candidates". Most of the information on the involvement of polymorphic gene variants in chronic multifactorial diseases comes from studies based on investigating associations of certain "candidate gene" variants with disease incidence or manifestations. The present review will be focused upon interactions of genetic background and diet with regard to the development of such life-threatening chronic conditions as cardiovascular disease (CVD) [7-9] and cancer [10-12] that are responsible for the majority of deaths in developed Western countries. The nature of these interactions is, indeed, very complex, and its investigation, and especially unbiased interpretation of the results is extremely difficult. Nevertheless there is a considerable body of published data that can already be critically analyzed at the present level of our knowledge.

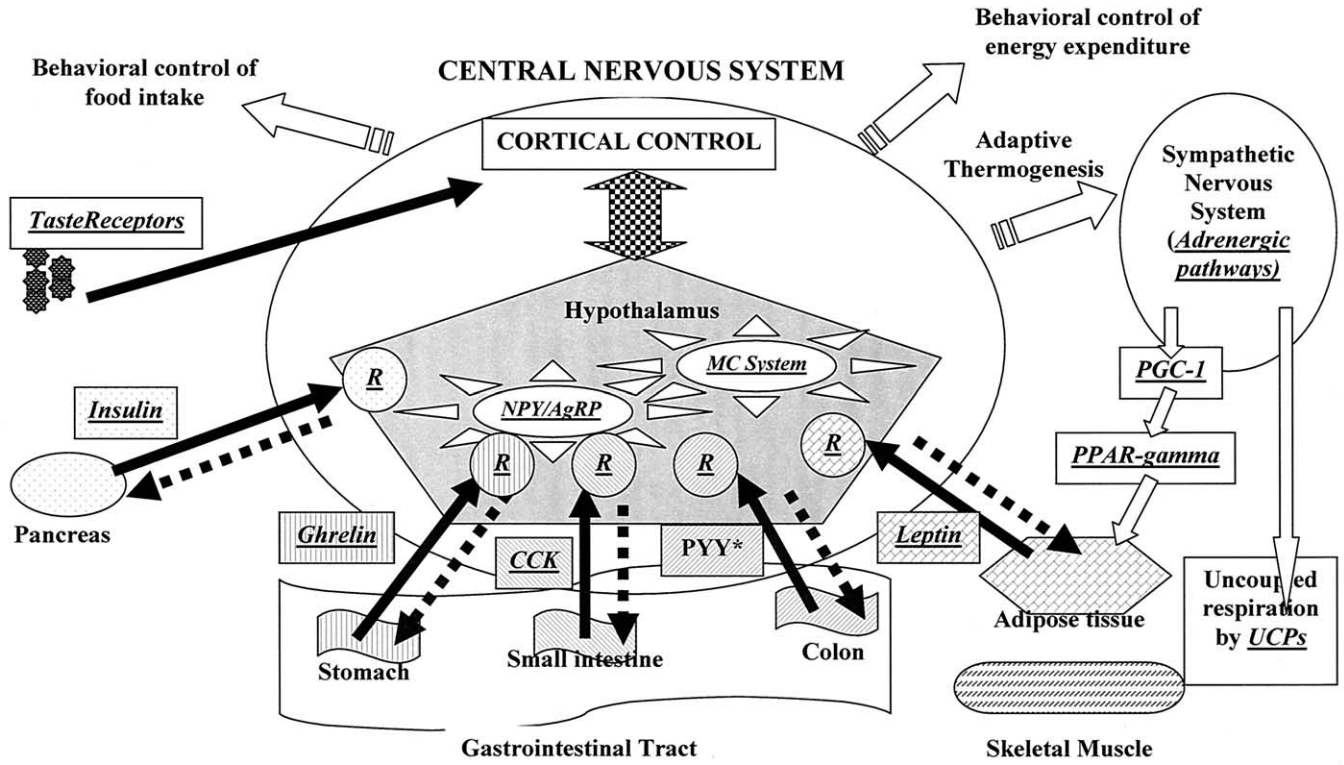

Fig. 2. Gene polymorphisms in the regulatory pathways controlling energy homeostasis. Peripheral signaling factors (**Insulin, Leptin, Ghrelin, CCK, PYY**) interact through their specific receptors (**R**) with central regulatory networks (**NPY/AgRP** and **MC** systems) triggering complex cortex-mediated responses directing energy intake and expenditure. Polymorphic genes encode most of the proteins involved in these cascade processes, thus substantial degree of interindividual variation can be expected. Polymorphic factors are shown in Italic and underlined. Dashed arrows designate feedback control pathways. **NPY** –Neuropeptide Y; **AgRP**–Agouti-related protein; **MC System**–Melanocortin system; **CCK**–Cholecystokinin; **PYY**-peptide $YY_{3-36;}$ **PGC-1**-Peroxisome proliferator-activated receptor-gamma-coactivator-1; **PPAR–gamma** - Peroxisome proliferator-activated receptor-gamma; **UCPs** –uncoupling proteins. **R**-s on different backgrounds designate corresponding receptors. ***** - PYY_{3-36} is not shown to be polymorphic since no information on its variants was available at the time of preparation of the review.

2. Energy balance regulation, deregulation, and obesity: a diet-related pathway to the development of chronic diseases. Role of gene polymorphisms

In the developed Western countries obesity is certainly the commonest nutrition-related disorder. Being a serious independent health problem, obesity is also believed to be the core element of a group of metabolic abnormalities that has recently been defined as metabolic syndrome, which also commonly includes insulin resistance and hyperinsulinemia, hypertension, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus [13]. It is generally accepted that obesity and associated metabolic anomalies dramatically increase risk of developing a variety of chronic diseases including CVD and cancer [14-16].

Diet is the crucial environmental factor in the development of obesity. Overeating in combination with low physical activity is the main cause of the obesity epidemic rapidly spreading in the modern world [14]. It is, however, clear that individual susceptibility to obesity strongly depends on the genetically determined patterns of energy balance regulation. Therefore it is important to start consideration of the problem of gene-nutrient interactions from its key point of genetic control of mechanisms regulating human food intake and energy homeostasis.

2.1. Genes encoding factors regulating food/energy intake

Basic mechanisms governing food intake involve extremely complex cooperation of peripheral signaling mechanisms and central nervous system that integrates information flows generated by multiple feedback loops monitoring blood levels of certain nutrients, signals from chemo- and mechanoreceptors of gastrointestinal tract, and responds preserving adequate balance between energy intake and expenditure [17]. Fig. 2 presents a simplified scheme of these regulatory mechanisms. It should be noted that regulation of energy intake in humans is strongly affected by numerous psychosocial phenomena ranging from simple taste differences (food preferences) [18] to religious customs and social influences [19]. For this reason human obesity that is often caused by regular deliberate overeating can be regarded both as a (patho-)physioliologic and a behavioral phenomenon. Although genetic variation may affect the both mechanisms, still obscure area of human behavioral genetics is beyond the scope of this review.

Differences in food preferences existing between individuals are generally well known, and their development can be observed from first years of life [20]. Discussions on the genetic basis of these differences continued for a long time [18,20], but identification of the relevant genes has started only recently, when a novel family of 40-80 human and rodent G protein-coupled receptors expressed in taste receptor cells of the tongue and palate epithelia has been identified [21]. These putative mammalian taste receptors called T2Rs have been shown to function as bitter taste receptors [21,22]. Several recent reports also indicate T1R family as putative receptors for sweet taste [23,24]. Studies on the genetic basis of taste were initiated using models involving sweet-sensitive and sweet-insensitive strains of mice, and it is interesting that Max et al. have found a specific Tas1r3 gene polymorphism assorting between taster and non-taster mouse strains [24]. No information on the polymorphisms of the human homologue genes (T1R family) is yet available, however the existence of coding single-nucleotide polymorphisms (SNPs) in human T2R genes encoding bitter taste receptors has already been reported [25]. Rapid progress in this area of research promises to provide long-awaited understanding of genetic mechanisms controlling formation of food preferences, thus allowing dietary counseling and intervention to be appropriately designed and targeted [26]. Presently known polymorphisms in the taste receptor genes are shown in Table 1.

Food preferences, albeit influential for individual selection of diet constituents, do not define quantitative aspects of food intake, which are particularly important in terms of obesity risk. It was generally accepted that hypothalamic and brain stem centers are involved in the regulation of food intake and energy balance in humans [17], but information on the relevant regulatory factors and their genes was scarce before the last decade. Insulin remained the only candidate for the key role in body weight regulation for a long time [27]. It has recently been shown that polymorphisms in the regulatory sequence of its gene may be associated with juvenile obesity [28], however the influence did not look very strong. Other recently characterized factors now attract more attention in connection with obesity. One of the most interesting discoveries of the last decade was the identification of leptin. This cytokine-like peptide primarily expressed in adipocytes is now believed to be among the key regulators of fat metabolism and energy balance. Leptin is the product of the human homologue of mouse "obese" gene, homozygous mutation of which (ob/ob) causes synthesis of a defective and unstable leptin molecule, which results in hereditary obesity in mice [29]. Although the "ob/ob"-associated mouse obesity is a monogenic hereditary condition, studies in humans have hitherto failed to find leptin or any other mutant gene to be the unique "obesity gene". Conversely, multifactorial pattern involving action of numerous polymorphic gene products now looks more likely. Multiple polymorphisms and mutations within leptin gene sequence have been described [30,31]. Some of them, especially those located within upstream regulatory sequences of the gene, have been shown to be associated with altered leptin levels [33,33] and obesity [31,33], the (-2548)A/A variant clearly increasing diet-related obesity risk [34]. Even more attention has been paid to the leptin receptor gene, first identified in 199535. The gene, which encodes several alternatively spliced variants of the receptor, is polymorphic as well, and recent reports describe associations between some of its variants and obesity, fat distribution, insulin levels, and blood pressure (see Table 1).

Several factors synthesized in the gastrointestinal tract act alongside leptin and insulin as hormones strongly affecting food intake (see Fig. 2). They include ghrelin (orexigenic peptide mainly produced in the stomach) [46], cholecystokinin (produced in the small intestine and acting as a short-duration "satiety" signal) [47], and peptide $YY_{3\text{-}36}$ (produced in the colon and suppressing appetite for up to 12 hr) [48]. Exploration of these signaling pathways has just started, but it is already becoming clear that polymorphisms in the relevant genes may have important functional consequences. One SNP in the highly polymorphic ghrelin gene was found to be associated with fat accumulation [51] (Table 1). Diverse pathophysiologic manifestations have been reported for polymorphisms in the genes encoding cholecystokinin and its receptors (Table 1). At the same time genes encoding ghrelin receptor, peptide $YY_{3\text{-}36,}$ and its receptor Y2 (also acting as one of neuropeptide Y receptors) are not sufficiently investigated for the presence of polymorphic sites.

The mechanisms participating in the realization of the effects of leptin and other hormones on food intake and body weight regulation are now becoming clearer. Certain areas of the hypothalamus are rich in specific receptors binding the hormones and triggering central regulatory mechanisms. Factors acting at the central nervous system level include neuropeptide Y (NPY), corticotropin releasing hormone (CRH), proopiomelanocortin, α-melanocyte stimulating hormone, agouti-related protein, melanin-concentrating hormone (MCH), cocaine- and amphetamine-regulated transcript (CART), and probably some other peptides [58]. Interactions between them involving complex neuronal mechanisms eventually influence behavior and provide important links with neuroendocrine regulation of other vital functions of the organism. Evidence is accumulating that most (probably all) of the genes encoding central peptide factors mentioned here are polymorphic as well (Table 1), therefore there is a strong genetic background for considerable interindividual functional variability.

NPY is released from the arcuate hypothalamic nucleus in situations associated with fasting and hypoglycemia, and its secretion undergoes a feedback inhibition after food intake [17]. The Leu 7Pro polymorphism in the *NPY* gene has been shown to be implicated in lipid metabolism regulation. The Pro7 variant presence is a suspected cardiovascular risk factor in Caucasians [59,61,62], but has no importance in Japanese because of its extremely low frequency

Table 1
Gene polymorphisms affecting regulation of food intake and energy homeostasis

Gene	Polymorphisms	Reported functional/pathologic importance
Gene encoding taste receptors involved in the regulation of food preferences		
Bitter taste receptor *T2R3* gene	1 silent SNP [25]	Not reported
Bitter taste receptor *T2R4* gene	Four coding SNPs (missense mutations) [25]	Not reported
Bitter taste receptor *T2R5* gene	One coding SNP (miisense mutation) [25]	Not reported
Genes encoding factors involved in central regulation of food intake and energy homeostatis		
Insulin gene	VNTR in the 5′-untranslated region (position −596) [28].	The 5′-untranslated region VNTR is associated with fasting insulin levels and development of juvenile obesity [28].
Leptin (*Ob*)	Several rare coding region mutations ans SNPs; At least six common and nine less common 5′-untranslated region [30,31] polymorphisms.	Some of the 5′-untranslated region polymorphisms (in particular +19 and −2548) are associated with altered leptin levels [32,33] and obesity [31,33]. A/A(−2548) presence was shown to increase diet-related obesity risk [34].
Leptin receptor (*Ob-R*) gene	At least nine coding sequence polymorphisms (common: Lys109Arg, Gln223Arg, Lys656Asn) [36–39]; a pentanucleotide insertion/deletion polymorphism in the 3′-untranslateed region [40,41].	The Arg223 variant (especially homozygotes) is associated with increased adiposity [42,43]. Less convincing evidence links other polymorphic variants with obesity [37,39], fat distribution [43] regulation, insulin level regulation [41,44], and blood pressure regulation [45].
Ghrelin gene	At least ten SNPs [49–51].	The Met(72) allele (Leu(72)Met polymorphism) appeared to be protective against fat accumulation [51].
Cholecystokinin (*CCK*) gene	A polymorphic short tanden repeat in the 5′-untranslated region [51], several SNPs in the 5′-untranslated and coding sequence [52,53].	Limited evidence on the association with mood disorders [51]. Smoking habit was found to be associated with the presence of the T(−45) allele (C(−45)T polymorphism) [54].
Cholecystokinin type-A (CCK type-A) receptor gene	Five coding sequence SNPs [55]; G(−128)T and A(−81)G SNPs in 5′-untranslated (promoter) region [56].	The T/T (−128), G/G(−81) hormozygocity was associated with a significantly higher percent of body fat [56].
Cholecystokinin type-B (CCK type-B) receptor gene	At least eight SNPs in the coding sequence and 5′-untranslated region [56].	No clear evidence for a role in the energy balance regulation.
Neuropeptide Y (*NPY*) gene	A common polymorphism Leu(7)Pro in the signal peptide of NPY [59]; Four other polymorphisms (3 SNPs and T10/T11) [60].	The Pro(7) is associated with increased cholesterol levels and blood pressure in obese subjects [59, 61], increased blood pressure [61], carotid atherosclerosis [61,62]. The Pro(7) appears to be one of the factors determining alcohol drinking habits [63].
Neuropeptide Y Y1 receptor (*NPYY1R*) gene	One common SNP in intron 1 [66].	Not reported
Neuropeptide Y Y5 receptor (*NPYY5R*) gene	One silent polymorphism within the coding sequence [67]; Three SNPs in the non-coding regions [68].	May contribute to susceptibility to obesity [68].
Corticotropin-releasing hormone (*CRH*) gene	Several 5′-untranslated region polymorphisms [74,75].	Glucocorticoid level regulation may be affected [75]. A role in the pathogenesis of obesity is suggested, but not hitherto investigated.
Proopiomelanocortin (*POMC*) gene	Multiple mutations and polymorphisms [76, 77].	Polymorphic variants were shown to be associated with serum leptin levels [78].
Agouti-related protein (*AGRP*) gene	SNPs in the 5′ promoter region [79], coding region [80,81], and 3′-untranslated region [82].	Transcription-modulating promoter polymorphism was shown to be associated with body mass index and type 2 diabetes risk [79]. Coding region SNPs associated with anorexia nervosa [83].
Melanocortin 1 receptor (*MC1R*) gene	At least 27 polymorphic variants [84].	Skin and hair colour determination [84,85]. Certain variants are associated with skin melanoma [85], non-melanoma skin cancer [84], and prostate cancer risk [86].
Melanocortin 3 receptor (*MC3R*) gene	SNPs in the 5′-untranslated region and coding region [87].	Not reported.

Table 1
Continued

Gene	Polymorphisms	Reported functional/pathologic importance
Melanocortin 5 receptor (*MC4R*) gene	Multiple coding sequence mutations and polymorphisms [81,88,89].	Some variants may be associated with obesity [81, 89,90].
Melanocortin 5 receptor (*MC5R*) gene	Five SNPs (four of them silent) in the coding region [91].	Association with obesity [90].
Cocaine- and amphetamine-regulated transcript (*CART*) gene	Multiple SNPs mainly in 5′-untranslated region [92] and 3′-untranslated region [93].	Some polymorphisms may be associated with obesity [93,94].

in Japan [64]. These observations indicate that the role of *NPY* polymorphisms may differ in different human populations. Experiments with NPY-deficient mice have demonstrated unaltered regulation of food intake and body weight in these animals [65]. It appears that NPY interacting with leptin, insulin and other regulatory peptides may control one of a few alternative parallel regulatory pathways, deficiency of which can be compensated. Common polymorphisms in the genes encoding NPY receptors [66-68] can present another source of variation in this signal system. NPY receptors certainly play a major role in mediating different NPY-induced effects [69-71], however physiological importance of these polymorphisms remains to be elucidated. Clearly, the action of hypothalamic neuropeptides often has multiple endpoints. In this connection the participation of NPY in the control of blood pressure [72] and heart rate [73] is particularly intriguing, providing another link between the regulation of food intake and cardiovascular function that can be important for CVD development. Interestingly, associations with hypertension have already been described for polymorphic variants of both leptin and NPY receptor genes (see Table 1).

Table 1 shows several other polymorphic genes encoding factors that exert central regulation of food intake. The complexity and multiplicity of their functions is not yet fully understood, but should not be underestimated. For instance, polymorphisms in the genes encoding components of the melanocortin system also affect the regulation of pigment distribution [82,84,85], whereas variants of the melanocortin 1 receptor (MC1R) appear to be associated with several types of cancer [84-86]. On the other hand central regulation of food intake acts as an inseparable part of overall behavior regulation, thus being a subject of various controlling influences. It is apparent now that numerous gene polymorphisms strongly influence human behavior through structural and functional variation of neuromediators, their receptors, transporters, enzymes etc. Nevertheless, addressing this fascinating area is beyond limits of the present review. Interested readers can find information regarding gene polymorphisms involved in behavioral regulation and pathogenesis of multifactorial psychiatric disorders in recent reviews published elsewhere [95,96].

2.2. Genes encoding factors exerting energy expenditure regulation

Physical activity and adaptive thermogenesis are two main components of energy expenditure that present special interest in relation to obesity. This review is not aiming to address genetic aspects of physical activity control since it involves immensely complex interactions of behavioral stimuli generated by central nervous system and secondary responses of various “peripheral” physiological mechanisms, especially neuromuscular, respiratory and cardiovascular reactions. There is little doubt that gene polymorphisms may play major roles in the regulation of physical activity, however an unambiguous interpretation of presently available information is extremely difficult. An impressive example of this type of association has been provided by observations on the relationship between insertion/deletion (I/D) polymorphism of angiotensin converting enzyme (*ACE*) gene and physical endurance. It is now well proven that the presence of the “I” variant corresponding to lower ACE activity enhances metabolic efficiency leading to an increased physical endurance [97]. Nevertheless, ACE, being a component of circulatory homeostasis preservation, should be regarded together with other factors related to cardiovascular system, therefore the role of its polymorphism in physical endurance appears to be secondary. This example illustrates difficulties with genetic approaches to physical activity regulation that is not going to be further discussed in this review.

The adaptive thermogenesis in humans is closely related to the active mobilization of lipids from the fat cells. Central neural pathways exerting regulation of food intake and energy expenditure are tightly interrelated [98], and polymorphic factors acting at the central level have already been addressed in the previous subsection. As peripheral transmission of central regulatory stimuli to the fat stores is mediated by sympathetic nervous system, genes encoding adrenergic receptors (adrenoceptors) have attracted considerable attention as a gene family encoding factors participating in energy expenditure regulation [99], which could have a pathogenetic role in the development of obesity. Table 2 shows that a number of studies revealed functionally important polymorphisms in these genes. Several

Table 2
Gene polymorphisms affecting peripheral regulation of energy expenditure.

Gene	Polymorphisms	Reported functional/pathologic importance
Genes encoding adrenoceptors		
Alpha(2A)-adrenoceptor gene	An 18bp deletion [100].	Not reported.
Alpha(2B)-adrenoceptor gene	A deletion of 3 glutamic acids from a glutamic acid repeat element (Glu × 12, 297–309). Long [Glu(12)] and short [Glu(9)] alleles [101].	The Glu(9) may be associated with lower metabolic rate [101], and may contribute to the pathogenesis of obesity [101,102].
Beta(1)-adrenoceptor gene	Gly389Arg polymorphism [103].	Association with obesity [103].
Beta(2)-adrenoceptor gene	Common variants Gly16Arg and Gln27Glu; Rare polymorphism Thr164Ile [104].	Association with obesity reported for the Gln27Glu [34, 105] and Gly16Arg [34]. The Gly16Arg was shown to alter protein function [105].
Beta(3)-adrenoceptor gene	Common polymorphism Trp64Arg [106–108].	The Arg64 was associated with lower basal metabolic rate [106,109] and obesity [102,107,108,110]. The synergism in accelerating obesity was reported for the Arg64 in combination with the G(−3826) in UCP-1 gene [111–113].
Uncoupling protein 2 (*UCP2*) gene	Common polymorphisms Ala55Val [123], and a 45-bp deletion/insertion in the 3′-untranslated region of exon 8 [124]; rare Ala232Thr SNP [125]; five promoter region polymorphisms [126].	Val55 allele (especially Val/Val) was shown to be associated with an enhanced metabolic efficiency [127]. The exon 8 deletion/insertion polymorphism appeared to be associated with childhood-onset obesity [128]. G(−866)A associated with obesity risk [126].
Uncoupling protein 3 (*UCP3*) gene	Several mutations, at least seven polymorphisms [124,129–132].	The C(−55)T polymorphism was associated with BMI in obese subjects (TT genotype corresponded to a higher BMI) and appeared to be a factor modifying effects of physical activity [131,133]. The (−55)TT genotype was also shown to be associated with higher plasma cholesterol concentrations [134]. The G/A exon 6-splice donor junction polymorphism affected fat oxidation rates [130]. The GAIVS6 microsatellite polymorphism was associated with body composition and exercise efficiency [132].
Genes encoding transcription factors affecting adipocyte differentiation		
Peroxisome proliferator-activated receptor-gamma 2 (*PPARγ2*) gene	Common polymorphism Pro12Ala [136]. Silent exon 6 SNP His478His (C1431T) [136]. Pro115Glu mutation [137].	Association with obesity has been shown for the Pro115Glu mutation [137]. The 12A1a allele is consistently associated with a reduced risk of type 2 diabetes, whereas associations with obesity and blood lipid level control remain to be proven [138].
Peroxisome proliferator-activated receptor-gamma-coactivator-1 (*PGC-1*) gene	At least eight polymorphisms [140,141].	A common Gly482Ser polymorphism was found to be associated with type 2 diabetes risk [140].
C/EBP transcription factor family (α, β, δ) genes	Several mutations and polymorphisms [145,146].	Not reported.

groups reported an association of the Arg64 allele of the beta [3]-adrenoceptor gene with obesity. Common polymorphisms of the beta [2]-adrenoceptor gene have been found to alter the protein function and promote obesity (see Table 2). Some authors, however, failed to reproduce these findings and further confirmation is needed. The role of adrenoceptor genes and their variants in human obesity has been reviewed in more detail by Arner and Hoffstedt [99].

Whereas beta-adrenoceptors participate in the regulation of adaptive thermogenesis as a component of sympathetic nervous system, the ultimate control and modulation of heat-generating uncoupled respiration at the mitochondrial level is exerted by uncoupling proteins (UCPs) [98,114]. Initially this function was attributed to the uncoupling protein UCP1 found predominantly in brown adipocytes [114]. The role for the UCP1 in adult humans is still unclear, but several studies have shown that a 5′ region polymorphism of its gene appears to be associated with the development of obesity, acting synergistically with beta [3]-adrenoceptor gene coding sequence polymorphism [111,113] (Table 2). The recent identification of two other polymorphic members of the UCP family in humans (widely expressed in many tissues UCP2 [119] and brown adipose tissue- and muscle-specific UCP3 [120-122] resulted in additional observations of the effects of variation in the respective genes on body mass regulation (see Table 2). It should, however, be noted that studies in this direction have been started only four-five years ago, and results obtained by different groups analyzing functional significance of UCP polymorphisms are often controversial. At present only the C(-55)T polymorphism of

the UCP3 gene can be reliably regarded as a factor affecting fat distribution [131,133] probably by modifying the benefits of physical activity. The (-55)T/T homozygotes were also shown to have elevated plasma total cholesterol and LDL cholesterol concentrations [134]. Further analysis of the role of UCP gene polymorphisms, especially in combination with the assessment of adrenoceptor gene variants certainly looks promising in terms of revealing combinations important for pathogenesis of obesity and related chronic diseases.

The last group of genes to be considered in connection with peripheral regulation of energy expenditure comprises those encoding transcription factors affecting adipogenesis and adipocyte differentiation. The central place in this group belongs to peroxisome proliferator-activated receptor gamma (PPARγ) [135], especially its adipose tissue-specific isoform PPARγ2. This gene is much better studied compared to other genes of this group (Table 2). It has been reported that Pro115Glu mutation of *PPARγ2* gene is associated with severe obesity [137], however this mutation is rare. More attention has been paid to a common polymorphism Pro12Ala. The 12Ala variant is now believed to provide a reduced risk of type 2 diabetes [138], but the role of this polymorphism in obesity development and blood lipid level regulation remains to be confirmed. One interesting observation suggests that the ratio of dietary polyunsaturated fat to saturated fat influences the effect of the Pro12Ala polymorphism on BMI and fasting insulin levels [139], thus highlighting the importance of analyzing dietary factors in relation with numerous genetic polymorphisms affecting energy homeostasis. Little is known about polymorphisms in the genes encoding other factors governing adipocyte differentiation, in particular CCAT/enhancer-binding proteins (C/EBPs) [135,142,143] and adipocyte determination and differentiation-dependent factor 1/sterol regulatory element-binding protein 1 (ADD1/SREBP1) [135,144]. The absence of information does not allow excluding chances of existence of physiologically important polymorphisms in these genes, and recent observations of multiple SNPs in *CEBPα* [145] and *CEBPβ* [146] gene sequences support this suggestion.

In conclusion of this part of the review it should be emphasized that most of the factors involved in the regulation of energy homeostasis have been identified and characterized (in many cases only partially) within the last several years. Clearly, information regarding polymorphisms in the genes encoding key signaling and regulatory proteins is incomplete, and relationships of the gene variants with the development of major pathologic conditions need to be properly studied. It can be suggested that dietary factors exert strong modulating influences on these relationships, but firm evidence is still meagre. Presently there are more questions than answers in this emerging area, however its exceptional importance is already clear. Intensification of research linking genetic variation in the basic systems governing energy balance with pathogenesis of multifactorial chronic diseases is becoming an urgent problem.

Many other polymorphic genes are now known to be associated with both risk and clinical manifestations of several important diseases. The author perfectly understands that some reasonable limits should be imposed upon detailed description of all related problems. Therefore further discussion is going to be restricted with two most important groups of chronic multifactorial conditions, CVD and cancer.

3. Gene polymorphisms, diet, and cardiovascular disease

Cardiovascular (and cerebrovascular) disease or CVD can be characterized as a group of multifactorial conditions associated with atherosclerosis, hypertension, and thrombosis. All these pathologic entities are known to be closely related to both genetic factors and environmental influences. Strong relationship between diet composition and CVD risk is well established [7-9]. Obesity per se is a major cardiovascular risk factor, thus polymorphic genes involved in energy balance control that were discussed in the previous section of this review certainly provide “favorable” or “unfavorable” background for the development of CVD. Genes affecting other important pathogenetic pathways will be considered in this section.

3.1. Genes encoding factors involved in atherosclerosis development

Atheroscerosis undoubtedly constitutes the key element in the pathogenesis of CVD. In general atherosclerosis can be regarded as a complex combination of lipid transport and metabolism disorder with chronic inflammation [8,147]. Unlike in some other multifactorial conditions, especially cancer, risk of atherosclerosis can be detected at preclinical stages by relatively simple quantitative assessment of blood lipid profiles. Permanently elevated plasma levels of total cholesterol, LDL cholesterol, and triglycerides predispose to the development of atherosclerotic plagues, whereas increased HDL cholesterol levels appear to be protective. Availability of these reliable quantitative criteria allowed to discover strong links between dietary factors, especially saturated fat intake, and CVD risk [7-9]. On the other hand search for genetic factors involved in lipid transport and metabolism was greatly facilitated. For these reasons polymorphic genes affecting atherosclerosis development are considered here in more detail compared to those involved in blood pressure, hemostasis, and homocysteine metabolism regulation.

The utilization of dietary fat for its various biological functions in the organism would be impossible without a sophisticated system of lipid transport and metabolism, multiple components of which are highly polymorphic.

Genes encoding lipid transport proteins, their receptors, and lipid-processing enzymes are listed in Table 3. Virtually all of them display substantial variability, and in many instances specific polymorphisms were shown to be associated with characteristic changes in blood lipid concentrations. The role of gene polymorphisms affecting lipid transport and metabolism has been addressed in several recent reviews [148,150,155,156,162,189]. For this reason only selected important points of the problem are going to be considered here.

3.1.a. Genes encoding lipid transport proteins

Lipid transport proteins include multiple apolipoproteins, cholesteryl ester transport protein (CETP), phospholipid transport protein (PLTP), microsomal triglyceride transport protein (MTP), and fatty acid transport protein (FATP1). Known polymorphisms in the corresponding genes and their functional significance are presented in Table 3. It is obvious that there is abundant evidence linking many coding or regulatory sequence polymorphisms commonly present in human populations with specific changes in blood lipid concentration patterns and CVD risk. Furthermore, influences of polymorphic gene variants on diet-related changes in plasma lipid levels were reported in many instances. Nevertheless, the overall picture is far from being clear since conflicting results are frequently published by different groups. At present reliable positive evidence linking variants of the genes encoding lipid transport proteins with diet-related changes in serum lipid levels and cardiovascular risk exists only for the apolipoprotein E (*APOE)* gene [150,162] and probably for the *APOAI-APOCIII-APOAIV* gene cluster [149,150].

The *APOE* gene appears to be especially interesting because of its multifinctionality. Its common alleles ($\varepsilon 2$, $\varepsilon 3$ and $\varepsilon 4$) are defined by the presence of two SNPs within exon 4 of the gene. It is now proven that the $\epsilon 4$ variant is associated with elevated plasma levels of total and LDL cholesterol. Moreover it has been shown that individuals bearing this allele (even heterozygotes) may be more vulnerable to undesirable effects of fat-rich diet [150,163]. The $\epsilon 4$ allele is now regarded as an established CVD risk factor [150,162]. It is interesting that the same variant is closely associated with both increased risk and earlier onset of Alzheimer's disease [162]. At the same time the APOE appears to be involved in enterohepatic metabolism of cholesterol and bile acids [162]. It has also been shown to affect cell proliferation, immunoregulation, angiogenesis, and probably neoplastic growth [162].

Another example of interaction between diet and gene polymorphisms in lipid level control is coming from studies of the *APOAI-APOCIII-APOAIV* gene complex located on chromosome 11q. The three genes are known to be related by common regulatory mechanisms [148-150]. There is sufficient evidence indicating that several polymorphisms within this gene cluster affect blood lipid concentrations in a diet-dependent manner [148-151]. Nevertheless it is still difficult to reach real understanding of the combined effects of these polymorphisms (haplotype effects) since most studies have been focused on selected gene variants due to multiplicity of polymorphic sites and limitations imposed by insufficient study size.

Evidence linking other polymorphic genes encoding lipid transport proteins with diet-associated CVD risk looks fragmentary at the present level of our knowledge (see Table 3), however they are being studied very intensively, and major breakthroughs in this area may be expected in the near future.

3.1.b. Genes encoding lipoprotein receptors

Less information is available for the genes of this group (see Table 3). LDL receptor (*LDLR*) gene is an exception since it has attracted wide attention in connection with familial hypercholesterolemia, a monogenic hereditary condition caused by mutations of the *LDLR* gene. The gene is highly variable, and there are reports linking its polymorphisms with altered blood lipid levels [148,172]. *LDLR* gene shares extensive homology with a family of LDL receptor related protein (*LRP)* genes. Detailed investigation of polymorphisms in these complex genes encoding highly multifunctional factors [182] is just starting. No information on CVD risk and dietary associations has yet been published. Likewise, multiple polymorphisms have been detected in the *SR-BI* and *VLDLR* genes, but their functional significance remains to be determined.

3.1.c. Genes encoding lipid/lipoprotein-processing enzymes

Genes of this group are highly polymorphic. Lipoprotein lipase (*LPL*) gene intron 8 polymorphism was shown to be associated with plasma triglyceride and HDL cholesterol concentrations in a diet-dependent manner [148,156,189]. HDL cholesterol concentrations are also affected by C(-514)T promoter polymorphism of the hepatic lipase (*HL*) gene. Paraoxonases (*PON*), albeit not strictly lipid-metabolising enzymes, are also included into this group. Associations with CVD risk have been found for several enzyme activity-affecting polymorphisms in both *PON1* and *PON2* genes [194,195,197]. It is important to note that PON1 activity may also be influenced by diet, in particular by antioxidant vitamines [198]. It has also been reported that a diet rich in vegetables, berries and fruit reduces PON1 activity, and the response is modulated by *PON1* genotype [199].

3.1.d. Genes encoding inflammation-related proteins

Inflammation is now believed to be the main mechanism responsible for the formation of atherosclerotic plagues [147]. Although dietary factors may be involved in modulating inflammatory reactions, such links are much less obvious than in lipid metabolism-related mechanisms of atherosclerosis. Genetic aspects of inflammation in atherosclerosis represent a distinct scientific area that has recently

Table 3
CVD-associated polymorphisms in the genes encoding proteins involved in lipid transport and metabolism.

a. Lipid transport protein genes		
Apolipoprotein A-I (*APOA-I*) gene	Multiple polymorphisms including a common 5′-promoter region SNP G(−75)A and +83 MspI +/− polymorphism in intron 1 [148,149].	Polymorphisms influence diet-dependent regulation of APOA-1 and HDL cholesterol blood levels [148–151].
Apolipoprotein A-II (*APOA-II*) gene	At least 14 silent SNPs and one (CA)n microsatellite in intron 2 [152].	(CA)n was shown to affect plasma APOA-II concentrations and HDL subfractions [152]. T(−265)C affected APOA-II concentration, was associated with postprandial VLDL metabolism and visceral fat accumulation [154].
Apolipoprotein A-IV (*APOA-IV*) gene	At least four variants including common polymorphisms Thr(347)Ser and Glu(360)His [149,155]).	Polymorphisms modulate diet-related changes in triglycerides and LDL-cholesterol concentrations. Associations with food intake regulation and adiposity have been reported [148,149, 155].
Apolipoprotein(a) (*apo(a)*) gene	Multiple polymorphisms [156].	Plasma concentrations of lipoprotein(a) and atherosclerosis risk are affected [156].
Apolipoprotein B (*APOB*) gene	Multiple mutations and polymorphisms [156].	Modulation of plasma apolipoprotein and lipid concentrations in response to diet [148,156,157].
Apolipoprotein C-II (*APOC-II*) gene	Several mutations and polymorphisms [158,159].	Triglyceride level control may be affected [156,158,159], however no convincing evidence is available.
Apolipoprotein C-III (*APOC-III*) gene	At least eight polymorphisms [149].	Several SNPs were shown to affect serum lipid concentrations (especially triglycerides) in response to diet [148,150].
Apolipoprotein C-IV (*APOC-VI*) gene	At least five SNPs [160].	Limited evidence in favor of modulating effects on triglyceride levels [160].
Apolipoprotein D (*APOD*) gene	Several mutations and polymorphisms appearing to be ethnicity-specific [161].	Polymorphism effect on serum lipid (HDL) and lipoprotein levels in African blacks has been reported [161].
Apolipoprotein E (*APOE*) gene	Multiple mutations and polymorphisms. Three common alleles (ε2, ε3, ε4) are defined by two SNPs resulting in Arg(112)Cys and Cys(158)Arg [148,156, 162]).	APOE has a wide range of functions [161]. Its polymorphic variants strongly affect serum lipid levels and influence diet-related responses [148,150,162,163]. The ε4 allele is a known CVD risk factor [148,156,162]. It is also associated with an increased risk of Alzheimer's disease [162]. The influence of the polymorphisms on colon cancer risk has been suggested [164].
Apolipoprotein H or beta 2-glycoprotein I (*APOH*) gene	Ser(88)Asn and Trp(316)Ser SNPs [165].	Polymorphisms affect plasma total and LDL cholesterol concentrations [166] and APOH levels [167].
Apolipoprotein J or clusterin (*APOJ*) gene	At least seven polymorphisms [168].	Codon 317 and codon 328 SNPs were associated with HDL cholesterol level control in African Blacks [169].
Cholesteryl ester transport protein (*CETP*) gene	At least 11 polymorphisms [170–172].	Promoter region (−629), intron 1, and intron 7 polymorphisms are associated with HDL plasma levels [148,170–172], particularly in relation to alcohol consumption [170].
Phospholipid transport protein (*PLTP*) gene	At least eight polymorphisms [173].	Not reported.
Microsomal triglyceride transfer protein (*MTP*) gene	At least seven SNPs (three in the 5′ promoter region and four coding sequence missense polymorphisms) [174].	Controversial associations between *MTP* polymorphisms and total cholesterol, LDL cholesterol, APOB, triglyceride levels and obesity have been reported [174–176].
Fatty acid transport protein 1 (*FATP1*) gene	One SNP in intron 8 [177].	Association with triglyceride levels was reported [177].
Intestinal fatty acid binding protein (*FABP2*) gene	Ala(54)Thr [178].	Affects body composition and insulin sensitivity in a diet-dependent manner [178].
b. Lipoprotein receptor genes		
LDL receptor (*LDLR*) gene	Multiple mutations and polymorphisms [148,156,172].	Homozygous mutations cause familial hypercholesterolemia [156]. Polymorphisms affect blood lipid levels [148,172]). This effect may be related to diet composition [148].
LDL receptor-related protein (*LRP*) family genes	Multiple polymorphisms [179–181].	LRPs are highly multifunctional [182]. No direct association of polymorphisms in *LRP* genes with CVD risk was reported.
Scavenger receptor class B type I (*SR-BI*) gene	At least five polymorphisms [183].	Associations with LDL-cholesterol and HDL-cholesterol levels was reported [183].
VLDL receptor (V*LDLR*) gene	At least 11 polymorphisms [184,185].	Association with lipoprotein (a) levels [186]. May be involved in vascular dementia [187].

Table 3
Continued

a. Lipid transport protein genes		
c. Lipid/lipoprotein-metabolising enzyme genes		
Lipoprotein lipase (*LPL*) gene	Numerous polymorphisms [172,188,189].	Strong evidence on diet-related influences on blood lipids (especially triglycerides and HDL-cholesterol) [148,156,189].
Hepatic lipase (*HL*) gene	Multiple SNPs [156,172,190,191].	Promoter SNP C(−514)T is associated with HDL-cholesterol level regulation [156,191]. Its effect depends on dietary fat intake [192].
Lecithin:cholesterol acyltransferase (*LCAT*) gene	Multiple mutations and polymorphisms [148,172,193].	HDL cholesterol concentration regulation may be affected [148,193]. No information is available on associations with diet.
Paraoxonase 1 (*PON1*) gene	At least 7 SNPs [194–196]).	Association with CVD risk, especially for Arg(192)Glu [194, 195]. Promoter SNPs change PON1 expression and may also affect CVD risk [197]. PON1 activity is diet-dependent and modulated by its gene variants [198,199].
Paraoxonase 2 (*PON2*) gene	Cys(311)Ser [194].	Shown to be associated with CVD risk interacting with *PON1* Arg(192)Glu [194].

been reviewed elsewhere [200]. A brief look at the polymorphic genes investigated in this connection shows that polymorphisms in such genes as those encoding tumor necrosis factors α and β (*TNF*α and *TNF*β), transforming growth factors β1 and β2 (*TGF*β*1* and *TGF*β*2*), interleukin 1 (*IL1*), interleukin 1 receptor antagonist (*IL1ra*), lipopolysacharide receptor CD14, P-selectin, E-selectin, and platelet endothelial cell adhesion molecule 1 (*PECAM1)* may be involved in modulating atherosclerosis-related inflammatory reactions. All these inflammation-related agents act in concert with immune reactions involving numerous polymorphic factors of the immune system. The latter area is certainly beyond the scope of this review, however major role of the immune system in the pathogenesis of atherosclerosis should never be forgotten.

3.2. Genes encoding factors involved in blood pressure regulation

Arterial hypertension constitutes an important pathogenetic element in CVD. It is now well understood that numerous genetic factors are involved in blood pressure regulation and some genetic patterns can be responsible for raising blood pressure, which characterizes essential (primary) hypertension [201]. As it was mentioned in the beginning of this review, hypertension is one of the components of the obesity-associated metabolic syndrome [13], and influence of dietary factors altering energy homeostasis appears to predispose to blood pressure elevation. Indeed, it is well known that the loss of weight in hypertensive obese individuals usually leads to simultaneous blood pressure decrease [202]. At the same time it is difficult to say that dietary risk factors predisposing to hypertension are well defined. Sodium chloride is the only exception, however blood pressure responses to increases and decreases in dietary salt intake may be heterogenous suggesting possible genetic predisposition [203].

Polymorphic genes implicated in blood pressure regulation have recently been considered in a comprehensive review by Luft [201]. Renin-angiotensin system genes including those encoding angiotensinogen (*AGT*), angiotensin converting enzyme (*ACE*), and aldosterone synthase (*CYP11B2*) have been studied intensively in relation to human hypertension. Although several groups reported associations between *AGT* polymorphisms and elevated blood pressure, other researchers failed to observe similar effects. Likewise, variants of the *ACE* gene that have been associated with the risk of miocardial infarction [204] and control of physical endurance [97] (see also section 2.1 of this review), displayed no strong links to blood pressure levels [201,204]. No evidence of interactions between polymorphic variants of these genes and dietary factors is available. Sodium transport/metabolism–related genes such as those encoding epithelial sodium channel (ENaC) subunits, adducin, and 11β-hydroxysteroid dehydrogenase are certainly of interest, given well-proven association between dietary salt intake and hypertension [203]. Several groups tried to establish links between polymorphisms in these genes and their participation in sodium accumulation that can provoke hypertension [201]. The number of these studies is, however, limited and their results lack consistency.

There are reports associating human hypertension with polymorphisms in some G-proteins (G protein β subunit, GNAS1) and adrenergic receptors (section 2.2 of this review), but evidence is not sufficient, hence it is difficult to separate specific influence on blood pressure from other biological effects of these polymorphisms.

Polymorphisms in genes encoding endothelium-associated factors such as endothelial nitric oxide synthase (*eNOS* or *NOS3*), endothelin-1, prostacyclin synthase have also been implicated to the pathogenesis of hypertension and CVD in general [201]. The importance of nitric oxide as a molecule with a variety of biological functions including antiatherogenic properties is well established. For this rea-

son nitric oxide synthase (NOS) has attracted a wide attention in relation to a number of pathologic conditions. Endothelial nitric oxide synthase gene (*NOS3*) has four polymorphisms [205], which are believed to modulate risk of hypertension and coronary heart disease [201,205-207]. Among these polymorphisms Glu [298]Asp, which affects basal nitric oxide production [208], has been especially strongly linked with coronary atherosclerosis and myocardial infarction [205,207,208]. At the same time possible relationship between *eNOS* variants and dietary factors remains obscure, however it is known that reduced nitric oxide bioavailability is a factor predisposing to atherogenesis in obese individuals [210]. It should also be noted that NOS is implicated in pathogenesis of several other major diseases including cancer (see below). This makes investigation of the functional role of polymorphic variants of its isoforms even more urgent.

3.3. Genes encoding factors of the hemostatic system

Thrombosis of arteries affected by atherosclerosis constitutes the main mechanism leading to acute coronary and cerebrovascular syndromes. Impaired balance of multiple factors constituting blood coagulation system can lead to hypercoagulative state increasing thrombosis probability. Both environmental and genetic factors are involved. It is suspected that diet, especially excessive fat ingestion can trigger postprandial hypercoagulative state [211]. Gene polymorphisms affecting hemostasis have been considered in two recent reviews [212,213], thus only a brief outline is presented hereafter.

Several groups of genes are important for hemostasis regulation. Polymorphic variants of genes encoding platelet surface glycoproteins (glycoprotein Ia-Iia, glycoprotein Ib-V-IX, glycoprotein Iib-IIIa) have been shown to affect platelet adhesion and aggregation. Some of the variants have been suggested as thrombosis risk factors, however further evidence is needed to confirm initial findings [213]. Genes encoding coagulation factors (fibrinogen, prothrombin, factor V, factor VII, factor VIII, factor XI, factor XII, factor XIII) display numerous mutations and polymorphisms [212,213]. Multiple polymorphisms in the three genes encoding α, β, and γ fibrinogen chains (especially in the fibrinogen β gene) have been identified and shown to be associated with plasma fibrinogen levels [212-214]. At the same time no association was found between these variants and cardiovascular disease risk [212-214]. Several variants have been identified in the prothrombin gene sequence. Among them the G20210A was found to be associated with an increased risk of venous thrombosis [213]. Polymorphisms in other coagulation-related genes displayed association with protective effects against miocardial infarction (Arg353Gln of factor VII and Val34Leu of factor XIII) [213], but these results also remain to be confirmed.

Blood coagulation is counterbalanced by the anticoagulant and fibrinolytic systems that also include polymorphic factors. Several groups observed effects of thrombomodulin gene variants on cardiovascular risks, but results were, again, inconsistent [213]. As regards thrombolytic system, several polymorphisms have been identified in the genes encoding tissue plasminogen activator (tPA) and plasminogen activator inhibitor I (PAI-I). The 4G variant of *PAI-I* insertion/deletion (4G/5G) promoter region polymorphism was associated with an increased risk of developing myocardial infarction [213]. It is interesting that the same 4G variant has recently been fount to be strongly associated with obesity [215]. PAI-I is a multifunctional factor, and it is going to be mentioned again in this review in connection with cancer.

3.4. Genes encoding factors controlling homocysteine metabolism

Hyperhomocysteinemia is now regarded as an independent risk factor in the development of cerebrovascular and coronary heart disease as well as venous thrombosis [216]. Both polymorphic variants of the enzymes involved in homocysteine metabolism and levels of the diet-originated vitamin co-factors of these enzymes affect serum homocysteine levels offering a good example of interaction between dietary factors and genetic background. Hyperhomocysteinemia may be caused by deficiencies of folate and vitamin B_{12} reducing homocysteine remethylation to methionine [216]. Vitamin B_6 deficiency affecting its catabolism is also regarded as a possible contributing factor [216]. The importance of this metabolic system is not limited by its association with CVD risk. Methionine production links it with both DNA methylation and protein synthesis, thus providing participation in developmental processes, tissue repair and neoplastic growth. Polymorphic genes encode several enzymes involved in folate metabolism and homocysteine generation. Methylenetetrahydrofolate reductase (MTHFR) is regarded as a key enzyme in this metabolic pathway. It is consistently proven that serum homocysteine concentration is affected by a common polymorphism C [667]T (Ala→Val) in the *MTHFR* gene [217,218]. The 667T variant is regarded as a candidate CVD risk factor [218,219], however the degree of its impact is still debated. It should, however, be noted that other polymorphic gene variants of potential importance for homocysteine level regulation have been uncovered by recent studies. It is obvious now that another common *MTHFR* variant, A [1298] C (Glu→Ala), also affects the enzyme activity and interacts with the C [667]T polymorphism [220]. Simultaneous assessment of the two sites has been reported, but this study has failed to reveal any clear relationship to the CVD risk [221]. The *MTHFR* is certainly the best characterized candidate gene within homocysteine-related metabolic pathway, however recent studies rapidly expand the scope of the search. Multiple mutations and polymorphisms have been identified in the genes encoding methionine synthase (*MTR*) [222], methionine synthase reductase (*MTRR*) [223], cysta-

thionine β synthase (*CBS*) [224], glutamate carboxypeptidase II (*GCPII*) [225,226], thymidilate synthase (*TS*) [227], and transcobalamin (*TC*) [228]. It is reasonable to believe that complex polygenic mechanisms interacting with dietary influences are involved in the regulation of serum homocysteine levels, however further large-scale studies are needed to investigate them.

It is obvious that the amount of information on the polymorphic genes affecting CVD risk has dramatically increased within a very short period of time. Despite this impressive accumulation of information the present stage of our knowledge can be defined as a fragmentary collection of isolated facts, some of which are proven better than others. The real understanding of the relationship between multiple polymorphic gene variants, dietary factors and CVD risk and pathogenesis is still a long way ahead.

4. Gene polymorphisms, diet, and cancer

Unlike CVD, human sporadic malignancies do not offer any biomarker reliably predicting forthcoming disease. Histopathologic confirmation remains the ultimate diagnostic tool in oncology, however it can only be applied to already existing tumors. Successful identification by positional cloning of gene mutations responsible for the development of several rare monogenic familial tumor syndromes [6] strongly stimulated search for genetic markers of cancer risk. Unfortunately positional cloning that was so successful for monogenic conditions could not be used for the analysis of sporadic cancers characterized by truly multifactorial pathogenesis. For this reason investigation of candidate gene polymorphisms related to cancer risk was especially intense. Numerous attempts to assess effects of dietary factors in combination with genetic background have been made with different degrees of success. It is now accepted that diet is very important for the development of tumors of several sites, colorectal cancer risk being the most affected [11], however interactions between common gene variants and dietary influences are still poorly understood. The amount of literature published in the field is huge, and many comprehensive reviews are available [229-237]. Therefore a relatively brief outlook is going to be given here.

4.1. Genes encoding enzymes involved in xenobiotic metabolism

For a long timestudies of polymorphic genes relevant to cancer have been focused almost exclusively on the metabolic pathways controlling detoxification of exogenous chemical carcinogens [229]. Diet could be incorporated into this approach as a source of either carcinogens (intrinsic or cooking-generated) present in certain foods or constituents acting in a protective manner (vitamins, antioxidants, detoxifying enzyme-activating substances etc.) [230]. It is clear that carcinogen metabolism-affecting (commonly called "metabolic") polymorphisms may modify probability of contact between carcinogens and target cells, thus acting at the stage of cancer initiation. It is perfectly understandable that the efforts to identify functionally important polymorphisms of this type have been closely related to both investigation of carcinogenesis induced by exogenous (environmental) agents and cancer chemoprevention through dietary modifications.

Enzymes related to xenobiotic metabolism are divided into two major groups, exerting Phase I and Phase II metabolism of exogenous compounds. Phase I reactions often leading to exogenous procarcinogen metabolic activation are mainly catalyzed by cytochrome P450 (CYP) family of enzymes. Numerous polymorphisms in the *CYP* genes (*CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP2E1*) have been studied for the last decade, however their importance for carcinogenesis still remains to be proven [231,232]. Likewise, studies of the genes encoding Phase II enzymes involved in detoxification of exogenous substances and products of Phase I reactions provided only limited evidence of cancer risk-modulating effects. Recent detailed reviews considering polymorphisms in genes encoding N-acetyltransferases (*NAT1* and *NAT2*) [233], glutathione S-transferases (*GSTM1, GSTM3, GSTT1,* and *GSTP1*) [234,235], NAD(P)H:quinone oxidoreductase (*NQO1*) [236], and microsomal epoxide hydrolase (*mEH*) [237] all indicate lack of reliable positive evidence probably due to complexity of genetic and metabolic interactions. In this situation incorporation of dietary data into analysis of associations between metabolic polymorphisms and cancer risk often led to controversial results, hence most of the suggestions made on the risk-modulating effects of certain combinations of diet and gene variants need confirmation in further large-scale studies employing multigene analysis.

4.2. Genes encoding DNA repair enzymes

This group of polymorphic genes has recently emerged as another potentially important determinant of cancer initiation probability. Direct links between polymorphic variants of DNA repair-associated genes and dietary factors do not seem likely, although efficient repair of mutagenic lesions (e.g DNA adducts) resulting from action of carcinogens deriving from food certainly should be regarded as a factor. Association with cancer of different sites has been reported for polymorphic variants of the following genes encoding DNA repair enzymes: *XRCC1*(codon 399 polymorphism) [238-240], *XRCC3* [241,242], XPD [243,244], ERCC2 [245], *OGG1* [246,247], O^6-alkylguanine DNA alkyltransferase [248], cytosine DNA-methyltransferase-3B[249,] and mismatch repair genes (MSH2, MLH1, MSH6[r]) [232]. Information on the relationship between these gene variants and environmental factors is limited by reports on the effects of smoking.

4.3. Genes encoding factors involved in cell cycle regulation

Deregulation of the cell cycle in somatic cell populations can be regarded as one of the leading mechanisms of neoplastic growth resulting from mutations or gene expression alterations at somatic cell level. Nevertheless, common polymorphic variants of several genes encoding cell cycle-controlling proteins have recently been investigated in relation to cancer risk. Cyclin D1 gene polymorphism G870A has been shown to be associated with several types of cancer [250-252]. Cancer risk associations have been reported for polymorphisms in p21(Waf1/Cip1) cyclin-dependent kinase inhibitor [253] and prohibitin [254] genes. Polymorphisms in some oncogenes (*HRAS* VNTR minisatellite) [232] and tumor suppressor genes (*p53, APC*) [232] can also be included into this group. There are no reports directly linking these polymorphisms with dietary factors, however effects of such general mechanisms as energy homeostasis regulation or supply of simple molecules used for nucleic acid and protein synthesis seem to be very likely. Progress in this area deserves close attention since genetic variation in the regulation of cell proliferation and differentiation may be one of the basic mechanisms underlying differences in probability and aggressiveness of neoplastic growth in different individuals.

4.4. Genes encoding factors involved in hormonal regulation

Influences of these gene polymorphisms are most strongly manifested in hormone dependent tumors such as breast, prostate, ovarian and endometrial cancers. Polymorphisms in sex hormone receptor genes comprising those encoding estrogen receptor, progesterone receptor, androgen receptor have been shown to be associated with cancer risk modulation. Likewise, a number of polymorphic genes encoding enzymes involved in steroid metabolism including steroid 5α-reductase type 2(*SRD5A2*), 3β-hydroxysteroid dehydrogenases 1 and 2(*HSD3B1* and *HSD3B2*), catechol-O-methyltransferase *(COMT*), *CYP17,* and *CYP19.* Most of these polymorphisms have been considered in two recent reviews in relation to breast [255] and prostate [256] cancers. Dietary factors can certainly interact with hormonal regulation. Obesity, which has been considered in the first section of this review, strongly affects hormonal status. At the same time some food components, such as phytoestrogens are known to be processed by the same metabolic pathways as sex hormones [257], thus their cancer-preventive effect can be modulated by the polymorphisms mentioned here.

4.5. Genes encoding enzymes related to DNA methylation

This group of genes has already been discussed in relation to folate/homocysteine metabolism and heart disease risk. Folate and/or methyl group dietary supply is directly linked to DNA methylation [258], especially in the CpG-dinucleotide–rich regions, which are common in regulatory sequences. For this reason polymorphic genes encoding enzymes of the folate metabolic pathway may influence DNA methylation and modulate gene expression, being closely involved both in normal growth and differentiation and in associated disorders including neoplasia. Polymorphic *MTHFR* has attracted considerable attention as one of the main candidate genes in terms of modulating cancer risk through altered DNA methylation. There is now some direct evidence that the C [677]T polymorphism in the *MTHFR* gene affects genomic DNA methylation through an interaction with folate status [259]. Interactions between *MTHFR* gene variants and dietary folate availability are believed to be among cancer risk-affecting factors. Special attention has been paid to colorectal neoplasia risk, and it has been shown that individuals with the T/T677 *MTHFR* genotype are particularly strongly affected by dietary habits. This genotype may be a protective factor (compared to C/C or C/T variants) for those on a low risk diet (high folate or methionine and low alcohol), however a higher risk of developing colorectal tumors was reported in such individuals if they have a high-risk diet (low folate or methionine and high alcohol intake) [260]. This relationship, which clearly opens opportunities for active dietary prevention of colorectal cancer, constitutes one of the best examples of gene-nutrient interactions discovered so far. Less is known about the A1298C polymorphism in the *MTHFR* gene, however the C/C1298 genotype has been found to be associated with a slight reduction of colorectal cancer risk [261]. The *MTHFR* polymorphisms have also been shown to be associated with susceptibility to prostate cancer [262], esophageal carcinoma [263], and acute leukemia [264]. Limited information is available on other genes encoding enzymes related to this metabolic pathway. Nevertheless there are reports linking polymorphisms in methionine synthase [262,265,266], cystathionine β synthase [262,267], thymidilate synthase [266,268,269], and serine hydroxymethyltransferase [266] genes to neoplastic conditions.

4.6. Genes encoding factors involved in angiogenesis

Initial studies directed to uncovering relationship between polymorphic gene variants and neoplasia were focused mostly on metabolic and regulatory systems acting at the stage of cancer initiation. It is, however, evident that later events including tumor progression, invasion and metastatic spread are not less important. One of the determining elements of these later stages is tumor-associated angiogenesis that is connected with a distorted balance between diverse pro- and antiangiogenic factors [270,271], most of which are highly multifunctional. Among them members of the vascular endothelial growth factor (VEGF) and angiopoietin (Ang) families are believed to be crucial [271,272]. Reports regarding associations between *VEGF* gene poly-

morphisms and cancer development are just starting to emerge [273,274]. Several variants of the angiopoetin-2 gene have recently been described [275], however there is no information on functional and clinical importance of these polymorphisms. At the same time it is now clear that polymorphisms in multiple genes encoding other factors that are directly or indirectly involved in angiogenesis are often associated with clinical features of tumors in the affected individuals. Virtually all these genes have already been considered in this review in relation to CVD. Indeed, polymorphisms of several inflammation-related genes including *TNF* α[r] [274,276], *TGFβ1* [277], IL1B [278,279], *IL1RN* [279], IL8 [274], IL10 [274], have been shown to be important for several types of tumors. Polymorphisms in the *eNOS* gene are associated with the development of the lung [280], prostate [281], and ovarian [282] cancer. Although there is no doubt about the significance of the extracellular proteolysis mediated by plasminogen activation system for both angiogenesis and tumor invasion/metastasis, effects of polymorphisms in the related genes have not been studied. Our recent preliminary results indicate that *PAI-I* 4G/5G polymorphism may be associated with colorectal cancer prognosis [283], but further confirmation is needed. Finally, *APOE* gene has also been shown to be involved in angiogenesis regulation [162], however reports regarding possible role of its polymorphisms in carcinogenesis [164,284,285,] can also reflect other effects of the multifunctional protein encoded by this gene.

The regulation of angiogenesis is known to be strongly affected by dietary factors such as plant polyphenols [286], especially genistein [287], and fatty acids and their derivatives [288]. Relationship between these dietary influences and genetic variation modulating angiogenesis remains obscure. Development of studies in this direction is obviously important for unraveling pathogenesis of later stages of neoplasia. On the other hand significance of these links for physiological angiogenesis regulation and mechanisms of CVD development should not be underestimated.

4.7. Other genes

It is impossible to cover all examples of gene variation related to cancer in this review, but it appears to be important to return briefly to the problems of energy homeostasis regulation and cancer. It is well known that dietary restriction inhibits carcinogenesis in rodent models [289]. Obesity is certainly a risk factor for at least some cancers in humans [16], but investigation of the relationship between energy homeostasis-related gene polymorphisms and cancer pathogenesis has only entered its initial stage. Presently available information is scarce. Several groups reported associations between melanocortin 1 receptor (*MC1R*) gene and skin cancer [84], melanoma [85], and prostate cancer [86]. Polymorphisms in beta [2] and beta [3] adrenoceptor genes, which are involved in energy expenditure regulation, have been found to be associated with risk of breast [290] and colorectal [291] cancer development. Variants of differentiation-regulating *PPARγ* gene, which is closely related to adipogenesis [135], have been reported to be associated with endometrial and renal cell carcinoma [292]. It can be expected that other gene variants associated with energy balance regulation are going to emerge as players in the field of cancer susceptibility. Moreover, virtually nothing is known on the role of genetic factors in the development of such serious abnormalities of energy homeostasis related to advanced neoplasia as cancer-related anorexia and cachexia [293,294]. It is believed that deregulation of the homeostasis-controlling mechanisms that have been considered in the first section of this review is the main cause of these lethal phenomena, thus association of cancer cachexia risk with specific genetic variants appears to be very likely. Initiation of studies in this direction is an urgent problem.

Several other polymorphic genes such as those encoding vitamine D receptor, some cell adhesion molecules etc have also been implicated to cancer development, but it is impossible to discuss all these polymorphisms here. Likewise mechanisms of immune system interaction with neoplastic growth involving numerous polymorphic factors constitute an independent problem of great importance and are not considered in this review.

5. Candidate genes: existing problems and approaches to their solution

The analysis of recent literature has shown that the number of reports on polymorphic gene variants associated with multifactorial diseases is growing with dramatic speed. At the same time very few studies provide firm and reliable evidence of causative relationships between these polymorphisms and disease risk or pathogenesis. Indeed, in most studies possible effects of single gene variants were assessed in situations when combined impacts of multiple factors could be expected. Most of these multiple impacts had to be ignored for different reasons including limitations imposed by study size, insufficient knowledge on metabolic/regulatory pathways and respective genes involved, methodological difficulties etc. In any case, relatively weak (due to low penetrance) effects of single gene polymorphisms were difficult to detect in the presence of numerous interfering genetic (and environmental) variables. It can be assumed that analysis of combinations of gene variants encoding interacting factors within a biological chain or cascade, rather than isolated investigation of its single components, may have more chances to reveal real causative connections between gene polymorphisms and disease. The relationship between multifactorial diseases and complex combinations of genetic and environmental factors can be roughly described by the scheme presented in Fig. 3a. The scheme depicts four hypothetical diseases differently affected by all possible polymorphism combinations in a group of genes encoding interacting factors within some

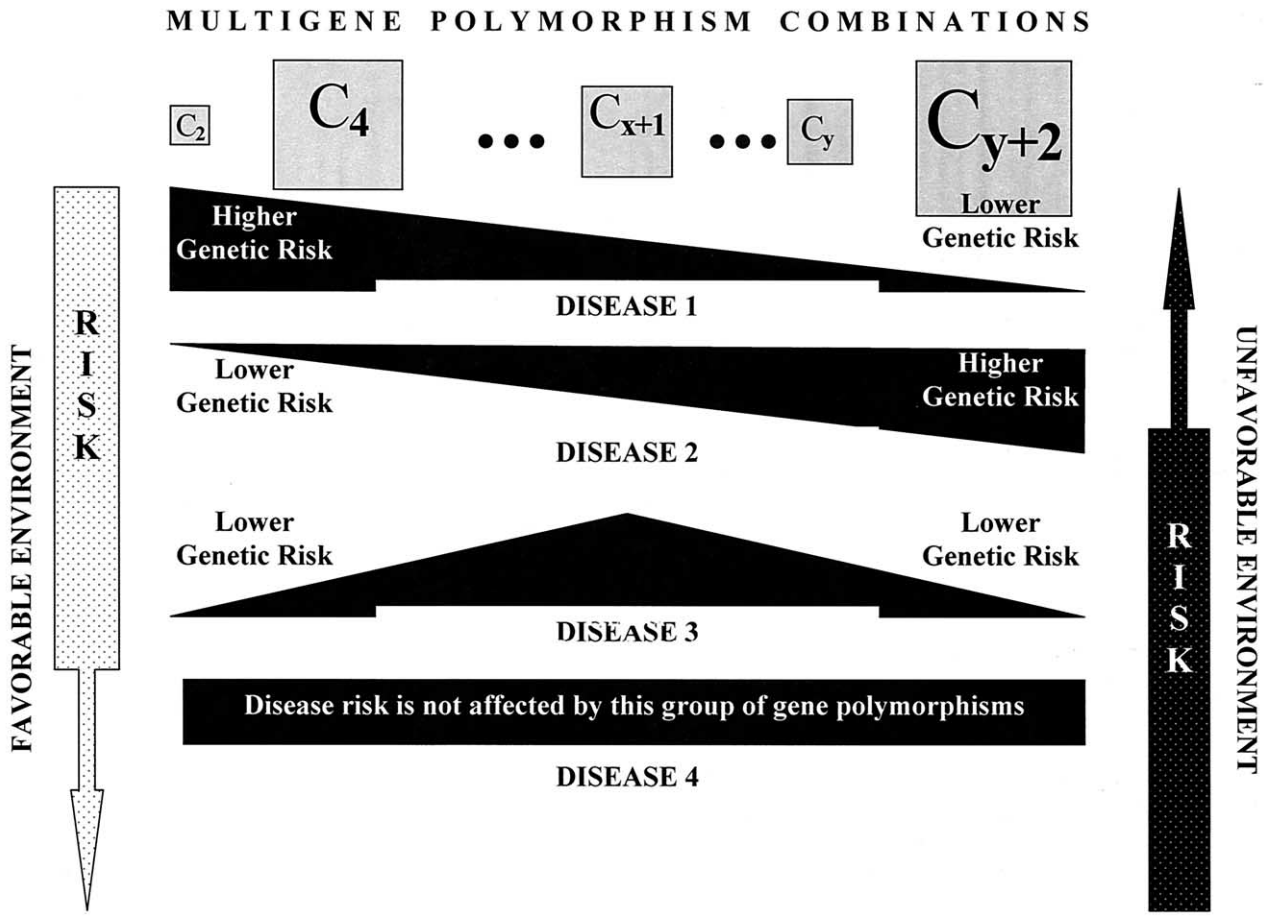

Fig. 3. Relationship between multigene polymorphism combinations, environmental factors, and multifactorial disease risk.Four hypothetical multifactorial conditions displaying different patterns of relationship between disease risk and a set of combinations of polymorphic variants in a group of functionally related genes are shown. Obviously, definitions of "favorable"/"unfavorable" environment may differ for different diseases. ($\mathbf{C}_n$ – genotype combinations; $x > 4$; $y > x + 1$)Two model situations are presented: a). Based on the assumption of independent allele segregation and equal probability of all variants to influence disease risk. b). Taking into account actual absence of many theoretically possible combinations, different allele/haplotype frequencies in populations, differences in functional significance between variants. Square sizes reflect relative importance ("weight") of certain genotype combinations.

regulatory or metabolic system. It should not be forgotten that certain gene variants (variant combinations) might predispose to some diseases, being at the same time protective against other conditions [290]. Thus, the C_1 combination in the Fig. 3 is associated with the highest genetic risk of the disease 1, being at the same time protective for the conditions 2 and 3, and not affecting the disease 4. Given virtually unlimited number of possible combinations of multiple polymorphisms in genes encoding various interacting factors (in case of independent allele segregation), elucidation of their combined functional significance may seem hopeless, however real number of relevant combinations appears to be much lower. Analysis of SNP distribution throughout human genome has shown existence of different patterns including regions of very low SNP incidence (SNP "deserts") and lengthy regions of linkage disequilibrium containing only a few haplotypes [296]. Moreover functional significance of different polymorphic variants and their combinations considerably differs, and frequencies of certain combinations widely vary in human populations, providing good opportunities for selecting most important patterns according to their functional role and frequency. Hence, Fig. 3b may better reflect the real situation.

Conflicting results obtained by different groups in association studies of the same candidate gene variants constitute a serious problem, which has provoked sharp criticism of the candidate gene approach [297]. However, careful study design based on strict epidemiological criteria may help to increase efficiency of candidate gene studies [297]. The selection of candidate genes and polymorphisms within them emerges as the key element of study design. In multigene studies it is always important to choose genes, products of which interact within regulatory or metabolic pathways. In most cases it is not realistic to analyze all possible gene variants and combinations, hence existing polymorphisms should be initially prioritized on the basis of their likelihood to affect function of the encoded product. Linkage disequilibrium, often associating alleles at adjacent loci [298], can allow reducing number of informative polymorphisms to analyze. Availability of biochemical confirmation

of functional significance of chosen polymorphism(s) is another important advantage. Similarly, complete and careful characterization (antropometric, clinical, biochemical etc) of phenotypic variants found among investigated cases and controls is always highly desirable. Separate targeted analysis of subgroups displaying specific phenotypic characteristics may provide better chances of revealing effects of gene variants. Finally, incorporation of additional environmental factors into analysis should be done upon thorough analysis of information on the metabolic and regulatory systems supposed to be affected by these factors. Sometimes, especially in diet-associated projects, pilot intervention studies employing groups of people preselected according to their genetic characteristics may provide extremely valuable information. Indeed, facing the perspective of large-scale expensive projects involving thousands of people, we have to accept that careful study design is the key element of success.

6. Conclusions and future directions

Materials presented in this review highlight serious problems and difficulties existing in the field of gene polymorphism analysis in relation to multifactorial diseases. Nevertheless there are examples of successful investigation of complex systems based on interaction of polymorphic gene variants with environmental factors. Analysis of folate metabolism-associated pathway eventually linked with DNA methylation has already allowed to uncover a system of interactions between dietary supply of folate and vitamins B_{12} and $B_{6,}$ gene polymorphisms, and pathogenesis of several multifactorial conditions including CVD and cancer. With this firm background there is little doubt that knowledge on this metabolic system is going to expand. These achievements are likely to fuel rapid progress in investigation of other systems, some of which now emerge as major new areas of the research in the field.

One of the most intriguing problems directly related to human chronic diseases, nutrition, and genetic variation is regulation of energy homeostasis. Some of its key elements have recently been discovered, and genetic variation in them is at least partially established. It can be concluded that the present level of knowledge already allows direct investigation of the role of interactions between nutrition and gene variation patterns in energy intake and expenditure control in relation to pathogenesis of complex multifactorial diseases. Most of the studies in this direction have hitherto been concentrated on the pathogenesis of obesity and diabetes mellitus, however it may be time to expand the scope of investigations addressing other chronic conditions as CVD and cancer. Assessment of lipid transport and metabolism-related gene variants is a closely related problem, which can probably benefit from integration with the general area of energy homeostasis control. Other important directions deserving close attention include investigation of genetic variation in regulation of angiogenesis, inflammatory reactions, and cell growth and differentiation (comprising control of the cell cycle, DNA repair, and DNA methylation). It can also be emphasized that the vast majority of researchers are still concentrating their efforts on identifying gene variants *predisposing* to pathologic conditions. Search for genetic traits *protecting* against multifactorial diseases should be given the same priority.

This review could not cover all immense area of gene variation in human disease. Such important fields as genetic variation in the immune system, psychiatric genetics, genetic mechanisms of diabetes mellitus could not be addressed, however the general idea of looking for roles for combinations of gene variants, rather than for single polymorphisms, can be expanded to these areas as well.

Diet-related mechanisms are not always obvious for the whole range of conditions considered in this review. It is, however, clear that dietary modification presents the easiest and probably the most efficient way to influence risk of many diseases at everyday lifestyle level. For this reason information regarding genetic variants affecting responses to dietary factors can considerably improve development of individualized preventive strategies and eventually prevent many untimely deaths. [57, 115–122, 153, 209, 241, 242, 245, 246, 247, 249, 276, 277, 278, 295]

References

[1] Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.
[2] Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science 2001;291:1304–51.
[3] Chakravarti A. Population genetics–making sense out of sequence. Nature Genet 1999;21:56–60.
[4] Risch NJ. Searching for genetic determinants in the new millennium. Nature 2000;405:847–56.
[5] Subramanian G, Adams MD, Venter JC, Broder S. Implications of the human genome for understanding human biology and medicine. JAMA 2001;286:3307–396.
[6] Collins FS. Positional cloning moves from perditional to traditional. Nature Genet 1995;91:347–50.
[7] Schaefer EJ. Lipoproteins, nutrition, and heart disease. Am J Clin Nutr 2002;75:191–212.
[8] Lusis AJ. Atherosclerosis. Nature 2000;407:233–41.
[9] Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Capps NE, Smith GD, Riemersma RA, Ebrahim, S. Dietary fat intake and prevention of cardiovascular disease: systemic review. Br Med J 2001;322:757–63.
[10] Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617–31.
[11] Potter JD. Colorectal cancer: Molecules and populations. J Natl Cancer Inst 1999;91:916–32.
[12] Rock CL, Lampe JW, Patterson RE. Nutrition, genetics, and risks of cancer. Ann Rev Publ Health 2000;21:47–64.
[13] Ukkola O, Bouchard C. Clustering of metabolic abnormalities in obese individuals: the role of genetic factors. Ann Med 2001;33: 79–90.
[14] Kopelman PG. Obesity as a medical problem. Nature 2000;404: 635–43.

[15] Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease–An update. Hypertension 2001;37:1053–9.
[16] Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565–74.
[17] Jéquier E, Tappy L. Regulation of body weight in humans. Physiol Rev 1999;79:451–80.
[18] Drewnowski A, Henderson SA, Barratt-Fornell A. Genetic taste markers and food preferences. Drug Metab Dispos 2001;29:535–8.
[19] Baranowski T, Cullen KW, Baranowski J. Psychosocial correlates of dietary intake: advancing dietary intervention. Ann Rev Nutr 1999; 19:17–40.
[20] Birch LL. Development of food preferences. Ann Rev Nutr 1999; 19:41–62.
[21] Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS. A novel family of mammalian taste receptors. Cell 2000;100: 693–702.
[22] Chandrashekar J, Mueller KL, Hoon MA, Adler E, Feng L, Guo W, Zuker CS, Ryba NJ. T2Rs function as bitter taste receptors. Cell 2000;100:703–11.
[23] Matsunami H, Montmayeur J-P, Buck LB. A family of candidate taste receptors in human and mouse. Nature 2000;404:601–4.
[24] Max M, Shanker YG, Huang LQ, Rong M, Liu Z, Campagne F, Weinstein H, Damak S, Margolskee RF. Tas1r3, encoding a new candidate taste receptor, is allelic to the sweet responsiveness locus Sac. Nature Genet 2001;28:58–63.
[25] Ueda T, Ugawa S, Ishida Y, Shibata Y, Murakami S, Shimada S. Identification of coding single-nucleotide polymorphisms in human taste receptor genes involving bitter tasting. Biochem Biophys Res Commun 2001;285:147–51.
[26] Patterson RE, Eaton DL, Potter JD. The genetic revolution: Change and challenge for the dietetics profession. J Am Diet Assoc 1999; 99:1412–20.
[27] McMinn JE, Baskin DG, Schwartz MW. Neuroendocrine mechanisms regulating food intake and body weight. Obes Rev 2000;1: 37–46.
[28] Le Stunff C, Fallin D, Schork NJ, Bougneres P. The insulin gene VNTR is associated with fasting insulin levels and development of juvenile obesity. Nature Genet 2000;26:444–6.
[29] Zhang YY, 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.
[30] Karvonen MK, Pesonen U, Heinonen P, Laakso M, Rissanen A, Naukkarinen H, Valve R, Uusitupa MIJ, Koulu M. Identification of new sequence variants in the leptin gene. J Clin Endocr Metab 1998;83:3239–42.
[31] Li WD, Reed DR, Lee JH, Xu W, Kilker RL, Sodam BR, Price RA. Sequence variants in the 5′ flanking region of the leptin gene are associated with obesity in women. Ann Hum Genet 1999;63:227–34.
[32] Hager J, Clement K, Francke S, Raison J, Lahlou N, Rich N, Pelloux V, Basdevant A, Guy-Grand B, North M, Froguel P. A polymorphism in the 5′ untranslated region of the human ob gene is associated with low leptin levels. Int J Obesity 1998;22:200–5.
[33] Mammes O, Betoulle D, Aubert R, Herbeth B, Siest G, Fumeron F. Association of the G-2548A polymorphism in the 5′ region of the LEP gene with overweight. Ann Hum Genet 2000;64:391–4.
[34] Nieters A, Becker N, Linseisen J. Polymorphisms in candidate obesity genes and their interaction with dietary intake of n-6 polyunsaturated fatty acids affect obesity risk in a sub-sample of the EPIC-Heidelberg cohort. Eur J Nutr 2002;41:210–21.
[35] Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J. Identification and expression cloning of a leptin receptor. OB-R. Cell 1995;83:1263–71.
[36] Echwald SM, Sorensen TD, Sorensen TIA, Tybjaerg-Hansen A, Andersen T, Chung WK, Leibel RL, Pedersen O. Amino acid variants in the human leptin receptor: Lack of association to juvenile onset obesity. Biochem Biophys Res Commun 1997;233:248–52.
[37] Thompson DB, Ravussin E, Bennett PH, Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. Hum Mol Genet 1997;6:675–9.
[38] Matsuoka N, Ogawa Y, Hosoda K, Matsuda J, Masuzaki H, Miyawaki T, Azuma N, Natsui K, Nishimura H, Yoshimasa Y, Nishi S, Thompson DB, Nakao K. Human leptin receptor gene in obese Japanese subjects: evidence against either obesity-causing mutations or association of sequence variants with obesity. Diabetologia 1997; 40:1204–10.
[39] Mammes O, Aubert R, Betoulle D, Pean F, Herbeth B, Visvikis S, Siest G, Fumeron F. LEPR gene polymorphisms: associations with overweight, fat mass and response to diet in women. Eur J Clin Invest 2001;31:398–404.
[40] Francke S, Clement K, Dina C, Inoue H, Behn P, Vatin V, Basdevant A, Guy-Grand B, Permutt MA, Froguel P, Hager J. Genetic studies of the leptin receptor gene in morbidly obese French Caucasian families. Hum Genet 1997;100:491–6.
[41] Oksanen L, Karpio J, Mustajoki P, Kontula K. A common pentanucleotide polymorphism of the 3′-untranslated part of the leptin receptor gene generates a putative stem-loop motif in the mRNA and is associated with serum insulin levels in obese individuals. Int J Obesity 1998;22:634–40.
[42] Chagnon YC, Wilmore JH, Borecki IB, Gagnon J, Perusse L, Chagnon M, Collier GR, Leon AS, Skinner JS, Rao DC, Bouchard C. Associations between the leptin receptor gene and adiposity in middle-aged Caucasian males from the HERITAGE family study. J Clin Endocr Metab 2000;85:29–34.
[43] Wauters M, Mertens I, Chagnon M, Rankinen T, Considine RV, Chagnon YC, Van Gaal LF, Bouchard C. Polymorphisms in the leptin receptor gene, body composition and fat distribution in overweight and obese women. Int J Obesity 2001;25:714–20.
[44] Wauters M, Mertens I, Rankinen T, Chagnon M, Bouchard C, Van Gaal L. Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. J Clin Endocr Metab 2001;86:3227–32.
[45] Rosmond R, Chagnon YC, Holm G, Chagnon M, Perusse L, Lindell K, Carlsoon B, Bouchard C, Bjorntorp P. Hypertension in obesity and the leptin receptor gene locus. J Clin Endocr Metab 2000;85: 3126–31.
[46] Horvath TL, Diano S, Sotonyi P, Heiman M, Tschop M. Minireview: ghrelin and the regulation of energy balance–a hypothalamic perspective. Endocrinology 2001;142:4163–9.
[47] Liddle RA. Regulation of cholecystokinin secretion in humans. J Gastroenterol 2000;35:181–7.
[48] Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY_{3-36} physiologically inhibits food intake. Nature 2002;418:650–4.
[49] Ukkola O, Ravussin E, Jacobson P, Snyder EE, Chagnon M, Sjostrom L, Bouchard C. Mutations in the preproghrelin/ghrelin gene associated with obesity in humans. J Clin Endocrinol Metab 2001; 86:3996–9.
[50] Korbonits M, Georguiev M, O'Grady E, Lecoeur C, Swan DC, Mein CA, Weill J, Grossman AB, Froguel P. A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. J Clin Endocrinol Metab 2002;87:4005–8.
[51] Ukkola O, Ravussin E, Jacobson P, Perusse L, Rankinen T, Tschop M, Heiman ML, Leon AS, Rao DC, Skinner JS, Wilmore JH, Sjostrom L, Bouchard C. Role of ghrelin polymorphisms in obesity based on three different studies. Obes Res 2001;10:782–91.
[52] Hattori E, Ebihara M, Yamada K, Ohba H, Shibuya H, Yoshikawa T. Identification of a compound short tandem repeat stretch in the 5′-upstream region of the cholecystokinin gene, and its association with panic disorder but not with schizophrenia. Mol Psychiatry 2001;6:465–70.

[53] Fujii C, Harada S, Ohkoshi N, Hayashi A, Yoshikawa K, Ishizuka C, Nakamura T. Association between polymorphism of the cholecystokinin gene and idiopathic Parkinson's disease. Clin Genet 1999; 56:394–9.
[54] Comings DE, Wu S, Gonzalez N, Iacono WG, McGue M, Peters WW, MacMurray JP. Cholecystokinin (CCK) gene as a possible risk factor for smoking: a replication in two independent samples. Mol Genet Metab 2001;73:349–53.
[55] Inoue H, Iannotti CA, Welling CM, Veile R, Donis-Keller H, Permutt MA. Human cholecystokinin type A receptor gene: cytogenetic localization, physical mapping, and identification of two missense variants in patients with obesity and non-insulin-dependent diabetes mellitus. Genomics 1997;42:331–5.
[56] Funakoshi A, Miyasaka K, Matsumoto H, Yamamori S, Takiguchi S, Kataoka K, Takata Y, Matsusue K, Kono A, Shimokata H. Gene structure of human cholecystokinin (CKK) type-A receptor: body fat content is related to CCK type-A receptor gene promoter polymorphism. FEBS Lett 2000;466:264–6.
[57] Tachikawa H, Harada S, Kawanishi Y, Okubo T, Shiraishi H. Novel polymorphism in the promoter and coding regions of the human cholecystokinin B receptor gene: an association analysis with schizophrenia. Am J Med Genet 1999;88:700–4.
[58] Barsh GS, Schwartz MW. Genetic approaches to studying energy balance: perception and integration. Nature Reviews (Genetics) 2002;3:589–600.
[59] Karvonen MK, Pesonen U, Koulu M, Niskanen L, Laakso M, Rissanen A, Dekker JM, T Hart LM, Valve R, Uusitupa MIJ. Association of a leucine(7)-to proline(7) polymorphism in the signal peptide of neuropeptide Y with high serum cholesterol and LDL cholesterol levels. Nature Med 1998;4:1434–7.
[60] Okubo T, Harada S. Polymorphism of the neuropeptide Y gene: An association study with alcohol withdrawal. Alcoholism–Clin Exp Res 2001;25S:59S–62S.
[61] Karvonen MK, Valkonen VP, Lakka TA, Salonen R, Koulu M, Pesonen U, Tuomainen TP, Kauhanen J, Nyyssonen K, Lakka HM, Uusitupa MIJ, Salonen JT. Leucine 7 to proline 7 polymorphism in the preproneuropeptide Y is associated with the progression of carotid atherosclerosis, blood pressure, and serum lipids in Finnish men. Atherosclerosis 2001;159:145–51.
[62] Niskanen L, Karvonen MK, Valve R, Koulu M, Pesonen U, Merkuri M, Rauramaa R, Toyry J, Laakso M, Uusitupa MIJ. Leucine 7 to Proline 7 polymorphism in the neuropeptide Y gene is associated with enhanced carotid atherosclerosis in elderly patients with type 2 diabetes and control subjects. J Clin Endocr Metab 2000;85:2266–9.
[63] Kauhanen J, Karvonen MK, Pesonen U, Koulu M, Tuomainen TP, Uusitupa MIJ, Salonen JT. Neuropeptide Y polymorphism and alcohol consumption in middle-aged men. Am J Hum Genet 2000;93: 117–21.
[64] Makino K, Kataoka Y, Hirakawa Y, Ikeda A, Yamauchi A, Oishi R. A leucine(7)-to-proline(7) polymorphism in the signal peptide of neuropeptide Y was not identified in the Japanese population. J Clin Pharmacy Therap 2001;26:201–3.
[65] Erickson JC, Clegg KE, Palmiter RD. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. Nature 1996;381:415–8.
[66] Herzog H, Baumgartner M, Vivero C, Selbie LA, Auer B, Shine J. Genomic organization, localization, and allelic differences in the gene for the human neuropeptide-Y Y1 receptor. J Biol Chem 1993;268:6703–7.
[67] Rozenkranz K, Hinney A, Ziegler A, von Prittwitz S, Barth N, Roth H, Mayer H, Siegfried W, Lehmkuhl G, Poustka F, Schmidt M, Schafer H, Remschmidt H, Hebebrand J. Screening for mutations in the neuropeptide Y Y5 receptor gene in cohorts belonging to different weight extremes. Int J Obesity 1998;22:157–63.
[68] Jenkinson CP, Cray K, Walder K, Herzog H, Hanson R, Ravussin E. Novel polymorphisms in the neuropeptide-Y Y5 receptor associated with obesity in Pima Indians. Int J Obesity 2000;24:580–4.
[69] Marsh DJ, Hollopeter G, Kafer KE, Palmiter RD. Role of the Y5 neuropeptide Y receptor in feeding and obesity. Nature Med 1998; 4:718–21.
[70] Pedrazzini T, Seydoux J, Kunstner P, Aubert JF, Grouzmann E, Beermann F, Brunner HR. Cardiovascular response, feeding behaviour and locomotor activity in mice lacking the NPY Y1 receptor. Nature Med 1998;4:722–6.
[71] Naveilhan P, Hassani H, Canals JM, Ekstrand AJ, Larefalk A, Chhajlani V, Arenas E, Gedda K, Svensson L, Thoren P, Ernfors P. Normal feeding behaviour, body weight and leptin response require the neuropeptide Y Y2 receptor. Nature Med 1999;5:1188–93.
[72] Michel MC, Rascher W. Neuropeptide Y–a possible role in hypertension. J Hypertens 1995;13:385–95.
[73] Beaulieu P, Lambert C. Peptidic regulation of heart rate and interaction with the autonomic nervous system. Cardiovasc Res 1998; 37:578–85.
[74] Baerwald CGO, Panayi GS, Lanchbury IS. Corticotropin releasing hormone promoter region polymorphisms in rheumatoid arthritis. J Rheumatol 1997;24:215–6.
[75] Rosmond R, Chagnon M, Bouchard C, Bjorntorp P. A polymorphism in the regulatory region of the corticotropin-releasing hormone gene in relation to cortisol secretion, obesity, and gene-gene interaction. Metabolism–Clin Experim 2001;50:1059–62.
[76] Hinney A, Becker I, Heibult O, Nottebom K, Schmit A, Ziegler A, Mayer H, Siegfried W, Blum WF, Remschmidt H, Hebebrand J. Systematic mutation screening of the pro-opiomelanocortin gene: Identification of several genetic variants including three different insertions, one nonsense and two missense point mutations in probands of different weight extremes. J Clin Endocr Metab 1998;83: 3737–41.
[77] Echwald SM, Sorensen TIA, Andersen T, Tybjaerg-Hansen A, Clausen JO, Pedersen O. Mutational analysis of the proopiomelanocortin gene in Caucasians with early onset obesity. Int J Obesity 1999;23:293–8.
[78] Hixson JE, Almasy L, Cole S, Birnbaum S, Mitchell BD, Mahaney MC, Stern MP, MacCluer JW, Blangero J, Comuzzie AG. Normal variation in leptin levels is associated with polymorphisms in the proopiomelanocortin gene, POMC. J Clin Endocr Metab 1999;84: 3187–91.
[79] Mayfield DK, Brown AM, Page GP, Garvey WT, Shriver MD, Argyropoulos G. A role for the Agouti-Related Protein promoter in obesity and type 2 diabetes. Biochem Biophys Res Commun 2001; 287:568–73.
[80] Brown AM, Mayfield DK, Volaufova J, Argyropoulos G. The gene structure and minimal promoter of the human agouti-related protein. Gene 2001;277:231–8.
[81] Dubern B, Clement K, Pelloux V, Froguel P, Girardet JP, Guy-Grand B, Tounian P. Mutational analysis of melanocortin-4 receptor, agouti-related protein, and alpha-melanocyte-stimulating hormone genes in severely obese children. J Pediatr 2001;139:204–9.
[82] Kanetsky PA, Swoyer J, Panossian S, Holmes R, Guerry D, Rebbeck TR. A polymorphism in the agouti signaling protein gene is associated with human pigmentation. Am J Hum Genet 2002;70:770–5.
[83] Vink T, Hinney A, van Elburg AA, van Goozen SHM, Sandkuijl LA, Sinke RJ, Herpertz-Dahlmann BM, Hebebrand J, Remschmidt H, van Engeland H, Adan RAH. Association between an agouti-related protein gene polymorphism and anorexia nervosa. Mol Psychiatry 2001;6:325–8.
[84] Bastiaens MT, ter Huurne JAC, Kielich C, Gruis NA, Westendorp RGJ, Vermeer BJ, Bavinck NJB. Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair. Am J Hum Genet 2001;68:884–94.
[85] Kennedy C, ter Huurne J, Berkhout M, Gruis N, Bastiaens M, Bergman W, Willemze R, Bavinck JNB. Melanocortin-1 (MC1R) receptor gene variants are associated with an increased risk for cutaneous melanoma which is largely independent of skin type and hair color. J Invest Dermatol 2001;117:294–300.

[86] Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RC. Prostate cancer risk: associations with ultraviolet radiation, tyrosinase and melanocortin-1 receptor genotypes. Br J Cancer 2001;85:1504–9.

[87] Li WD, Joo EJ, Furlong EB, Galvin M, Abel K, Bell CJ, Price RA. Melanocortin 3 receptor (MC3R) gene variants in extremely obese women. Int J Obesity 2000;24:206–10.

[88] Gu W, Tu ZM, Kleyn PW, Kissebah A, Duprat L, Lee J, Chin W, Maruti S, Deng NH, Fisher SL, Franco LS, Burn P, Yagaloff KA, Nathan J, Heymsfield S, Albu J, Pi-Sunyer FX, Allison DB. Identification and functional analysis of novel human melanocortin-4 receptor variants. Diabetes 1999;48:635–9.

[89] Rosmond R, Chagnon M, Bouchard C, Bjorntorp P. A missense mutation in the human melanocortin-4 receptor gene in relation to abdominal obesity and salivary cortisol. Diabetologia 2001;44: 1335–8.

[90] Chagnon YC, Chen WJ, Perusse L, Chagnon M, Nadeau A, Wilkison WO, Bouchard C. Linkage and association studies between the melanocortin receptors 4 and 5 genes and obesity-related phenotypes in the Quebec Family Study. Mol Medicine 1997;3:663–73.

[91] Hatta N, Dixon C, Ray AJ, Philips SR, Cunliffe WJ, Dale M, Todd C, Meggit S, Birch-Machin MA, Rees JL. Expression, candidate gene, and population studies of melanocortin 5 receptor. J Invest Dermatol 2001;116:564–70.

[92] Echwald SM, Sorensen TIA, Andersen T, Hansen C, Tommerup N, Pedersen O. Sequence variants in the human cocaine and amphetamine-regulated transcript (CART) gene in subjects with early onset obesity. Obesity Res 1999;7:532–6.

[93] Yamada K, Yuan X, Otabe S, Koyanagi A, Koyama W, Makita Z. Sequencing of the putative promoter region of the cocaine- and amphetamine-regulated-transcript gene and identification of polymorphic sites associated with obesity. Int J Obesity 2002;26:132–6.

[94] Challis BG, Yeo GSH, Farooqi IS, Luan J, Aminian S, Halsall DJ, Keogh JM, Wareham NJ, O'Rahilly S. The CART gene and human obesity–Mutational analysis and population genetics. Diabetes 2000;49:872–5.

[95] McGue M, Bouchard TJ. Genetic and environmental influences on human behavioral differences. Ann Rev Neurosci 1998;21:1–24.

[96] Stoltenberg SF, Burmeister M. Recent progress in psychiatric genetics–some hope but no hype. Hum Mol Genet 2000;9:927–35.

[97] Montgomery H, Clarkson P, Barnard M, Bell J, Brynes A, Dollery C, Hajnal J, Hemingway H, Mercer D, Jarman P, Marshall R, Prasad K, Rayson M, Saeed N, Talmud P, Thomas L, Jubb M, World M, Humphries S. Angiotensin-converting-enzyme gene insertion/deletion polymorphism and response to physical training. Lancet 1999; 353:541–5.

[98] Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. Cell 2001;104:531–43.

[99] Arner P, Hoffstedt J. Adrenoceptor genes in human obesity. J Intern Med 1999;245:667–72.

[100] Hamann A, Brieske C, Tafel J, Buttron P, Schwarzloh B, Munzberg H, Hinney A, Mayer H, Siegfried W, Hebebrand J, Greten H, Algenstaedt P, Ziegler R. Identification of a deletion variant in the gene encoding the human alpha(2A)-adrenergic receptor. Eur J Endocrinol 2001;144:291–5.

[101] Heinonen P, Koulu M, Pesonen U, Karvonen MK, Rissanen A, Laakso M, Valve R, Uusitupa M, Scheinin M. Identification of a three-amino acid deletion in the alpha (2B)-adrenergic receptor that is associated with reduced basal metabolic rate in obese subjects. J Clin Endocrinol Metab 1999;84:2429–33.

[102] Dionne IJ, Turner AN, Tchernof A, Pollin TI, Avrithi D, Gray D, Shuldiner AR, Poehlman ET. Identification of an interactive effect of beta(3)- and alpha(2b)-adrenoceptor gene polymorphisms on fat mass in Caucasian women. Diabetes 2001;50:91–5.

[103] Dionne IJ, Garant MJ, Nolan AA, Pollin TI, Lewis DG, Shuldiner AR, Poehlman ET. Association between obesity and a polymorphism in the beta(1)-adrenoceptor gene (Gly389Arg ADRB1) in Caucasian women. Int J Obesity 2002;26:633–9.

[104] Green SA, Turki J, Hall IP, Liggett SB. Implications of genetic variability of human β_2-adrenergic receptor structure. Pulm Pharmacol 1995;8:8–10.

[105] Large V, Hellstrom L, Reynisdottir S, Lonnqvist F, Eriksson P, Lannfelt L, Arner P. Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function. J Clin Invest 1997;100: 3005–13.

[106] Walston J, Silver K, Bogardus C, Knowler WC, Celi FS, Austin S, Manning B, Strosberg AD, Stern MP, Raben N, Sorkin JD, Roth J, Shuldiner AR. Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the beta 3-adrenergic-receptor gene. N Engl J Med 1995;333:343–7.

[107] Widen E, Lehto M, Kanninen T, Walston J, Shuldiner AR, Groop LC. Association of a polymorphism in the beta 3-adrenergic-receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 1995;333:348–51.

[108] Clement K, Vaisse C, Manning BS, Basdevant A, Guy-Grand B, Ruiz J, Silver KD, Shuldiner AR, Froguel P, Strosberg AD. Genetic variation of the beta 3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. N Engl J Med 1995;333:352–4.

[109] Sipilainen R, Uusitupa M, Heikkinen S, Rissanen A, Laakso M. Polymorphism of the beta(3)-adrenergic receptor gene affects basal metabolic rate in obese Finns. Diabetes 1997;46:77–80.

[110] Mitchell BD, Blangero J, Comuzzie AG, Almasy LA, Shuldiner AR, Silver K, Stern MP, MacCluer JW, Hixson JE. A paired sibling analysis of the beta-3 adrenergic receptor and obesity in Mexican Americans. J Clin Invest 1998;101:584–7.

[111] Clement K, Ruiz J, Cassard-Doulcier AM, Bouillaud F, Ricquier D, Basdevant A, Guy-Grand B, Froguel P. Additive effect of A→G (-3826) variant of the uncoupling protein gene and the Trp64Arg mutation of the beta 3-adrenergic receptor gene on weight gain in morbid obesity. Int J Obesity 1996;20:1062–6.

[112] Valve R, Heikkinen S, Rissanen A, Laakso M, Uusitupa M. Synergistic effect of polymorphisms in uncoupling protein 1 and beta(3)-adrenergic receptor genes on basal metabolic rate in obese Finns. Diabetologia 1998;41:357–61.

[113] Evans D, Minouchehr S, Hagemann G, Mann WA, Wendt D, Wolf A, Beisiegel U. Frequency and interaction between polymorphisms in the beta 3-adrenergic receptor and in uncoupling proteins 1 and 2 and obesity in Germans. Int J Obesity 2000;24:1239–45.

[114] Ricquier D, Fleury C, Larose M, Sanchis D, Pecqueur C, Raimbault S, Gelly C, Vacher D, Cassard-Doulcier AM, Levi-Meyrueis C, Champigny O, Miroux B, Bouillaud F. Contributions of studies on uncoupling proteins to research on metabolic diseases. J Intern Med 1999;245:637–42.

[115] Oppert JM, Vohl MC, Chagnon M, Dionne FT, Cassard-Doulcier AM, Ricquier D, Perusse L, Bouchard C. DNA polymorphism in the uncoupling protein (UCP) gene and human body fat. Int J Obesity 1994;18:526–31.

[116] Rousset S, Gonzales-Barroso MD, Gelly C, Pecqueur C, Bouillaud F, Ricquier D, Cassard-Doulcier AM. A new polymorphic site located in the human UCP1 gene controls the in vitro binding of CREB-like factor. Int J Obesity 2002;26:735–8.

[117] Esterbauer H, Oberkofler H, Liu YM, Breban D, Hell E, Krempler F, Patsch W. Uncoupling protein-1 m RNA expression in obese human subjects: the role of sequence variations at the uncoupling protein-1 gene locus. J Lipid Res 1998;39:834–44.

[118] Schaffler A, Pallitzsh KD, Watzlawek E, Drobnik W, Schwer H, Schlomerich J, Schmitz G. Frequency and significance of the A→G (-3826) polymorphism in the promoter of the gene for uncoupling protein-1 with regard to metabolic parameters and adipocyte transcription factor binding in a large population-based Caucasian cohort. Eur J Clin Invest 1999;29:770–9.

[119] Fleury C, Neverova M, Collins S, Raimbault S, Champigny O, Levi-Meyrueis C, Bouillaud F, Seldin MF, Surwit RS, Ricquier D, Waredn CH. Uncoupling protein-2: a novel gene linked to obesity and hyperisulinemia. Nature Genet 1997;15:223–4.
[120] Boss O, Samec S, Paolini-Giacobino A, Rossier C, Duloo A, Seydoux J, Muzzin P, Giacobino JP. Uncoupling protein-3: a new member of the mitochondrial carrier family with tissue-specific expression. FEBS Lett 1997;12:39–42.
[121] Vidal-Puig A, Solanes G, Grujic D, Flier JS, Lowell BB. UCP-3: an uncoupling protein homologue expressed preferentially and abundantly in skeletal muscle and brown adipose tissue. Biochem Biophys Res Commun 1997;235:79–82.
[122] Gong DW, He Y, Karas M, Reitman M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergetic agonists, and leptin. J Biol Chem 1997;272:24129–32.
[123] Urhammer SA, Dalgaard LT, Sorensen TI, Moller AM, Andersen T, Tybjaerg-Hansen A, Hansen T, Clausen JO, Vestergaard H, Pedersen O. Mutational analysis of the coding region of the uncoupling protein 2 gene in obese NIDDM patients: impact of a common amino acid polymorphism on juvenile and maturity forms of obesity and insulin resistance. Diabetologia 1997;40:1227–30.
[124] Walder K, Norman RA, Hanson RL, Schrauwen P, Neverova M, Jenkinson CP, Easlick J, Warden CH, Pecqueur C, Raimbault S, Ricquier D, Harper M, Silver K, Shuldiner AR, Solanes G, Lowell BB, Chung WK, Leibel RL, Pratley R, Ravussin E. Association between uncoupling protein polymorphisms (UCP2-UCP3) and energy metabolism/obesity in Pima Indians. Hum Mol Genet 1998;7:1431–5.
[125] Kubota T, Mori H, Tamori Y, Okazawa H, Fukuda T, Miki M, Ito C, Fleury C, Bouillaud F, Kasuga M. Molecular screening of uncoupling protein 2 gene in patients with noninsulin-dependent diabetes mellitus or obesity. J Clin Endocr Metab 1998;83:2800–4.
[126] Esterbauer H, Schneitler C, Oberkofler H, Ebenbichler C, Paulweber B, Sandhofer F, Ladurner G, Hell E, Strosberg AD, Patsch JR. A common polymorphism of UCP2 is associated with decreased risk of obesity in middle-aged humans. Nature Genet 2001;28:178–83.
[127] Astrup A, Toubro S, Dalgaard LT, Urhammer SA, Sorensen TIA, Pedersen O. Impact of the v/v 55 polymorphism of the uncoupling protein 2 gene on 24-h energy expenditure and substrate oxidation. Int J Obesity 1999;23:1030–4.
[128] Yanovski JA, Diament AL, Sovik KN, Nguyen TT, Li HZ, Sebring NG, Warden CH. Associations between uncoupling protein 2, body composition, and resting energy expenditure in lean and obese African American, white, and Asian children. Am J Clin Nutr 2000;71:1405–12.
[129] Schrauwen P, Xia J, Walder K, Snitker S, Ravussin E. A novel polymorphism in the proximal UCP3 promoter region: effect on skeletal muscle UCP3 mRNA expression and obesity in male nondiabetic Pima Indians. Int J Obesity 1999;23:1242–5.
[130] Argyropoulos G, Brown AM, Willi SM, Zhu JG, He YF, Reitman M, Gevao SM, Spruill I, Garvey WT. Effects of mutations in the human uncoupling protein 3 gene on the respiratory quotient and fat oxidation in severe obesity and type 2 diabetes. J Clin Invest 1998;102:1345–51.
[131] Otabe S, Clement K, Dina C, Pelloux V, Guy-Grand B, Froguel P, Vasseur F. A genetic variation in the 5′ flanking region of the UCP3 gene is associated with body mass index in humans in interaction with physical activity. Diabetologia 2000;43:245–9.
[132] Lanouette CM, Chagnon YC, Rice T, Perusse L, Muzzin P, Giacobino JP, Gagnon J, Willmore JH, Leon AS, Skinner JS, Rao DC, Bouchard C. Uncoupling protein 3 gene is associated with body composition changes with training in HERITAGE study. J Appl Physiol 2002;92:1111–8.
[133] Cassell PG, Saker PJ, Huxtable SJ, Kousta E, Jackson AE, Hattersley AT, Frayling TM, Walker M, Kopelman PG, Ramachandran A, Snehelatha C, Hitman GA, McCarthy MI. Evidence that single nucleotide polymorphism in the uncoupling protein 3 (UCP3) gene influences fat distribution in women of European and Asian origin. Diabetologia 2000;43:1558–64.
[134] Meirhaeghe A, Amouyel P, Helbecque N, Cottel D, Otabe S, Froguel P, Vasseur F. An uncoupling protein 3 gene polymorphism associated with a lower risk of developing type II diabetes and with atherogenic lipid profile in a French cohort. Diabetologia 2000;43:1424–8.
[135] Spiegelman BM, Flier JS. Adipogenesis and obesity: Rounding out the big picture. Cell 1996;87:377–89.
[136] Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. Biochem Biophys Res Commun 1997;18:270–4.
[137] Ristow M, Muller-Wieland D, Pfeiffer A, Krone W, Kahn CR. Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. N Engl J Med 1998;339:953–9.
[138] Altshuler D, Hirschhorn JN, Klannermark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES. The common PPAR gamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nature Genet 2000;26:76–80.
[139] Luan J, Browne PO, Harding AH, Halsall DJ, O'Rahilly S, Chatterjee VK, Warenham NJ. Evidence for gene-nutrient interaction at the PPARgamma locus. Diabetes 2001;50:686–9.
[140] Ek J, Andersen G, Urhammer SA, Gaede PH, Drivsholm T, Borch-Johnsen K, Hansen T, Pedersen O. Mutation analysis of peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1) and relationships of identified amino acid polymorphisms to Type II diabetes mellitus. Diabetologia 2001;44:2220–6.
[141] Esterbauer H, Oberkofler H, Linnemayr V, Igsleder B, Heddeger M, Wolfsburger P, Paulweber B, Fastner G, Krempler F, Patsch W. Peroxisome proliferator-activated receptor-gamma coactivator-1 gene locus: associations with obesity indices in middle-aged women. Diabetes 2000;51:1281–6.
[142] Roesler WJ. The role of C/EBP in nutrient and hormonal regulation of gene expression. Ann Rev Nutr 2001;21:141–65.
[143] Ramji DP, Foka P. CCAAT/enhancer-binding proteins: structure, function and regulation. Biochem J 2002;365:561–75.
[144] Kim JB, Wright HM, Wright M, Spiegelman BM. ADD1/SREBP1 activates PPAR-gamma through the production of endogenous ligand. Proc Natl Acad Sci USA 1998;95:4333–7.
[145] Gombart AF, Hofmann WK, Kawano S, Takeuchi S, Krug U, Kwok SH, Larsen RJ, Asou H, Miller CW, Hoelzer D, Koeffler HP. Mutations in the gene encoding the transcription factor CCAAT/enhancer binding protein alpha in myelodysplastic syndromes and acute myeloid leukemias. Blood 2002;99:1332–40.
[146] Vegesna V, Takeuchi S, Hoffmann WK, Ikezoe T, Tavor S, Krug U, Fermin AC, Heaney A, Miller CW, Koeffler HP. C/EBP-beta, C/EBP-delta, PU.1, AML1 genes: mutational analysis in 381 samples of hematopoietic and solid malignancies. Leuk Res 2002;26:459–60.
[147] Glass CK, Witztum JL. Atherosclerosis: The road ahead. Cell 2001;104:503–16.
[148] Ye SQ, Kwiterovich PO. Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol. Am J Clin Nutr 2000;52(5 Suppl.):1275S–84S.
[149] Groenendijk M, Cantor RM, de Bruin TW, Dallinga-Thie GM. The apoAI-CIII-AIV gene cluster. Atherosclerosis 2001;157:1–11.
[150] Ordovas JM, Schaefer EJ. Genetic determinants of plasma lipid response to dietary intervention: the role of the APOA1/C3/A4 gene cluster and the APOE gene. Br J Nutr 2000;83(Suppl. 1):S127–36.
[151] Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, Wilson PW, Scaefer EJ, Tucker K. Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on

HDL-cholesterol concentrations in a sex-specific manner: the Framingham Study. Am J Clin Nutr 2002;75:38–46.
[152] Fullerton SM, Clark AG, Weiss KM, Taylor SL, Stengard JH, Salomaa V, Boerwinkle E, Nickerson DA. Sequence polymorphism at the human apolipoprotein AII gene (APOA2): unexpected deficit of variation in an African-American sample. Hum Genet 2002;111: 75–87.
[153] Brousseau T, Dupuy-Gorce AM, Evans A, Arveiler D, Ruidavets JB, Haas B, Cambou JP, Luc G, Ducimetiere P, Amouyel P, Helbecque N. Significant impact of the highly informative (CA)n repeat polymorphism of the APOA-II gene on the plasma APOA-II concentrations and HDL subfractions: The ECTIM study. Am J Med Genet 2002;110:19–24.
[154] van't Hooft FM, Ruotolo G, Boquist S, de Faire U, Eggertsen G, Hamsten A. Human evidence that the apolipoprotein A-II gene is implicated in visceral fat accumulation and metabolism of triglyceride-rich lipoproteins. Circulation 2001;11:1123–8.
[155] Weinberg RB. Apolipoprotein A-IV polymorphisms, and diet-gene interactions. Curr Opin Lipidol 2002;13:125–34.
[156] Breslow JL. Genetics of lipoprotein abnormalities associated with coronary heart disease susceptibility. Ann Rev Genet 2000;34:233–54.
[157] Lopez-Miranda J, Ordovas JM, Ostos MA, Marin C, Jansen S, Salas J, Blanco-Molina A, Jimenez-Pereperez JA, Lopez-Segura F, Perez-Jimenez F. Dietary fat clearance in normal subjects is modulated by genetic variation at the apolipoprotein B gene locus. Arterioscler Thromb Vasc Biol 1997;17:1765–73.
[158] Sepehrnia B, Kamboh MI, Adams-Campbell LL, Bunker CH, Nwankwo M, Majumber PP, Ferrell RE. Genetic studies of human apolipoproteins. XI. The effect of the apolipoprotein C-II polymorphism on lipoprotein levels in Nigerian blacks. J Lipid Res 1989; 30:1349–55.
[159] Reina M, Brunzell JD, Deeb SS. Molecular basis of familial chylomicronemia: mutations in the lipoprotein lipase and apolipoprotein C-II genes. J Lipid Res 1992;33:1823–32.
[160] Kamboh MI, Aston CE, Hamman RF. DNA sequence variation in human apolipoprotein C4 gene and its effect on plasma lipid profile. Atherosclerosis 2000;152:193–201.
[161] Desai PP, Bunker CH, Ukoli FA, Kamboh MI. Genetic variation in the apolipoprotein D gene among African blacks and its significance in lipid metabolism. Atherosclerosis 2002;163:329–38.
[162] Mahley RW, Rall SC. Apolipoprotein E: Far more than a lipid transport protein. Ann Rev Genomics Hum Genet 2000;1:507–37.
[163] Loktionov A, Scollen S, McKeown N, Bingham SA. Gene-nutrient interactions: dietary behaviour associated with high coronary heart disease risk particularly affects serum LDL cholesterol in apolipoprotein E ϵ4-carrying free-living individuals. Br J Nutr 2000;84: 885–90.
[164] Kervinen K, Södervik H, Mäkelä J, Lehtola J, Niemi M, Kairaluoma MI, Kesäniemi YA. Is the development of adenoma and carcinoma in proximal colon related to apolipoprotein E phenotype? Gastroenterology 1996;110:1785–90.
[165] Sanghera DK, Kristensen T, Hamman RF, Kamboh MI. Molecular basis of the apolipoprotein H (beta 2-glycoprotein I) protein polymorphism. Hum Genet 1997;100:57–62.
[166] Kamboh MI, Bunker CH, Aston CE, Nestlerode CS, McAllister AE, Ukoli FA. Genetic association of five apolipoprotein polymorphisms with serum lipoprotein-lipid levels in African blacks. Genet Epidemiol 1999;16:205–22.
[167] Mehdi H, Aston CE, Sanghera DK, Hamann RF, Kamboh MI. Genetic variation in the apolipoprotein H (beta2-glycoprotein I) gene affects plasma apolipoprotein H concentrations. Hum Genet 1999;105:63–71.
[168] Tycko B, Feng L, Nguyen L, Francis A, Hays A, Chung WY, Tang MX, Stern Y, Sahota A, Hendrie H, Mayeux R. Polymorphisms in the human apolipoprotein-J/clusterin gene: ethnic variation and distribution in Alzheimer's disease. Hum Genet 1996;98:430–6.
[169] Nestlerode CS, Bunker CH, Sanghera DK, Aston CE, Ukoli FA, Kamboh MI. Apolipoprotein J polymorphisms and serum HDL cholesterol levels in African blacks. Hum Biol 1999;71:197–218.
[170] Corbex M, Poirier O, Fumeron F, Betoulle D, Evans A, Ruidavets JB, Arveiler D, Luc G, Tiret L, Cambien F. Extensive association analysis between the CETP gene and coronary heart disease phenotypes reveals several putative functional polymorphisms and gene-environment interaction. Genet Epidemiol 2000;19:64–80.
[171] Le Goff W, Guerin M, Nicaud V, Dachet C, Luc G, Arveiler D, Ruidavets JB, Evans A, Kee F, Morrison C, Chapman MJ, Thillet J. A novel cholesteryl ester transfer protein promoter polymorphism (-971G/A) associated with plasma high-density lipoprotein cholesterol levels. Interaction with the TaqIB and–629C/A polymorphisms. Atherosclerosis 2002;161:269–79.
[172] Knoblauch H, Bauerfeind A, Krähenbühl C, Daury A, Rohde K, Bejanin S, Essioux L, Schuster H, Luft FC, Reich JG. Common haplotypes in five genes influence genetic variance of LDL and HDL cholesterol in the general population. Hum Mol Genet 2002;11: 1477–85.
[173] Tahvanainen E, Jauhiainen M, Funke H, Vartiainen E, Sundvall J, Ehnholm C. Serum phospholipid transfer protein activity and genetic variation of the PLTP gene. Atherosclerosis 1999;146:107–15.
[174] Ledmyr H, Karpe F, Lundahl B, McKinnon M, Skoglund-Andersson C, Ehrenborg E. Variants of the microsomal triglyceride transfer protein gene are associated with plasma cholesterol levels and body mass index. J Lipid Res 2002;43:51–8.
[175] Couture P, Otvos JD, Cupples LA, Wilson PW, Scaefer EJ, Ordovas JM. Absence of association between genetic variation in the promoter of the microsomal triglyceride transfer protein gene and plasma lipoproteins in the Framingham Offspring Study. Atherosclerosis 2000;148:337–43.
[176] Juo SH, Han Z, Smith JD, Colangelo L, Liu K. Common polymorphism in promoter of microsomal triglyceride transfer protein gene influences cholesterol, ApoB, and trygliceride levels in young african american men: results from the coronary artery risk development in young adults (CARDIA) study. Arterioscler Thromb Vasc Biol 2000;20:1316–22.
[177] Meirhaeghe A, Martin G, Nemoto M, Deeb S, Cottel D, Auwerx J, Amoyel P, Helbecque N. Intronic polymorphism in the fatty acid transport protein 1 gene is associated with increased plasma triglyceride levels in a French population. Arterioscler Thromb Vasc Biol 2000;20:1330–4.
[178] Weiss EP, Brown MD, Shuldiner AR, Hagberg JM. Fatty acid binding protein-2 gene variants and insulin resistance: gene and gene-environment interaction effects. Physiol Genomics 2002;10: 145–57.
[179] McIlroy SP, Dynan KB, Vahidassr DJ, Lawson JT, Patterson CC, Passmore P. Common polymorphisms in LRP and A2M do not affect genetic risk for Alzheimer disease in Northern Ireland. Am J Med Genet 2001;105:502–6.
[180] Van Leuven F, Thiry E, Lambrechts M, Stas L, Boon T, Bruynseels K, Muls E, Descamps O. Sequencing of the coding exons of the LRP1 and LDLR genes on individual DNA samples reveals novel mutations in both genes. Atherosclerosis 2001;154:567–77.
[181] Okubo M, Horinishi A, Kim DH, Yamamoto TT, Murase T. Seven novel sequence variants in the human low density lipoprotein receptor related protein 5 (LPR5) gene. Hum Mutat 2002;19:186.
[182] Herz J, Strickland DK. LRP: a multifunctional scavenger and signaling receptor. J Clin Invest 2001;108:779–84.
[183] Acton S, Osgood D, Donoghue M, Corella D, Pocovi M, Cenarro A, Mozas P, Keilty J, Squazzo S, Woolf EA, Ordovas JM. Association of polymorphisms at the SR-BI gene locus with plasma lipid levels and body mass index in a white population. Arterioscler Thromb Vasc Biol 1999;19:1734–43.
[184] Sakai J, Hoshino A, Takahashi S, Muira Y, Ishii H, Suzuki H, Kawarabayasi Y, Yamamoto T. Structure, chromosome location,

and expression of the human very low density lipoprotein receptor gene. J Biol Chem 1994;269:2173–82.
[185] Near SE, Wang J, Hegele RA. Single nucleotide polymorphisms of the very low density lipoprotein receptor (VLDLR) gene. J Hum Genet 2001;46:490–3.
[186] Song J, Hong SH, Min W, Kim JQ. Association between triglyceride-rich lipoprotein remnant receptor polymorphisms and lipid traits. Clin Biochem 2000;33:441–7.
[187] Hellbecque N, Berr C, Cottel D, Fromentin-David I, Sazdovitch V, Ricolfi F, Ducimetiere P, Di Menza C, Amoyel P. VLDL receptor polymorphism, cognitive impairment, and dementia. Neurology 2001;56:1183–8.
[188] Templeton AR, Clarck AG, Weiss KM, Nickerson DA, Boerwinkle E, Sing CF. Recombinational and mutational hotspots within the human lipoprotein lipase gene. Am J Hum Genet 2000;66:69–83.
[189] Talmud PJ, Humphries SE. Genetic polymorphisms, lipoproteins and coronary artery disease risk. Curr Opin Lipidol 2001;12:405–9.
[190] van't Hooft FM, Lundahl B, Ragogna F, Karpe F, Olivecrona G, Hamsten A. Functional characterization of 4 polymorphisms in promoter region of hepatic lipase gene. Arterioscl Thromb Vasc Biol 2000;20:1335–9.
[191] Shohet RV, Vega GL, Bersot TP, Mahley RW, Grundy SM, Guerra R, Cohen JC. Sources of variability in genetic association studies: insights from the analysis of hepatic lipase. Hum Mutat 2002;19: 536–42.
[192] Ordovas JM, Corella D, Demissie S, Cupples LA, Couture P, Coltell O, Wilson PW, Schaefer EJ, Tucker KL. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. Circulation 2002;106:2315–21.
[193] Recalde D, Cenarro A, Garcia-Otin AL, Gomez-Coronado D, Civeira F, Pocovi M. Analysis of lipoprotein A-I, lecithin:acyltransferase and glucocerebrosidase genes in hypoalphalipoproteinemia. Atherosclerosis 2002;163:49–58.
[194] Sanghera DK, Aston CE, Saha N, Kamboh MI. DNA polymorphisms in two paraoxonase genes (PON1 and PON2) are associated with the risk of coronary heart disease. Am J Hum Genet 1998;62: 36–44.
[195] Heinecke JW, Lusis AJ. Paraoxonase gene polymorphisms associated with coronary heart disease: support for the oxidative damage hypothesis? Am J Hum Genet 1998;62:20–4.
[196] Brophy VH, Hastings MD, Clendenning JB, Richter RJ, Jarvik GP, Furlong CE. Polymorphisms in the human paraoxonase (PON1) gene promoter. Pharmacogenetics 2001;11:77–84.
[197] Leviev I, Poirier O, Nicaud V, Evans A, Kee F, Arveiler D, Morrisson C, Cambien F, James RW. High expressor paraoxonase PON1 gene promoter polymorphisms are associated with reduced risk of vascular disease in younger coronary patients. Atherosclerosis 2002; 161:463–7.
[198] Jarvik GP, Tsai NT, McKinstry LA, Wani R, Brophy VH, Richter RJ, Schellenberg GD, Heagerty PJ, Hatsukami TS, Furlong CE. Vitamin C and E intake is associated with increased paraoxonase activity. Arterioscl Thromb Vasc Biol 2002;22:1329–33.
[199] Rantala M, Silaste ML, Tuominen A, Kaikkonen J, Salonen JT, Alfthan G, Aro A, Kesaniemi YA. Dietary modifications and gene polymorphisms alter serum paraoxonase activity in healthy women. J Nutr 2002;132:3012–7.
[200] Andreotti F, Porto I, Crea F, Maseri A. Inflammatory gene polymorphisms and ischaemic heart disease: review of population association studies. Heart 2002;87:107–12.
[201] Luft FC. Hypertension as a complex genetic trait. Semin Nephrol 2002;22:115–26.
[202] Hermansen K. Diet, blood pressure, and hypertension. Br J Nutr 2000;83(Suppl. 1):S113–9.
[203] Luft FC, Weinberger MH. Heterogeneous responses to changes in dietary salt intake: the salt-sensitivity paradigm. Am J Clin Nutr 1997;65(2 Suppl.):612S–7S.
[204] Carluccio M, Soccio M, De Caterina R. Aspects of gene polymorphisms in cardiovascular disease: the renin-angiotensin system. Eur J Clin Invest 2001;31:476–88.
[205] Jeerooburkhan N, Jones LC, Bujac S, Cooper JA, Miller GJ, Vallance P, Humphries SE, Hingorani AD. Genetic and environmental determinants of plasma nitrogen oxides and risk of ischemic heart disease. Hypertension 2001;38:1054–61.
[206] Hyndman ME, Parsons HG, Verma S, Bridge PJ, Edworthy S, Jones C, Lonn E, Charbonneau F, Anderson TJ. The T-786→C mutation in endothelial nitric synthase is associated with hypertension. Hypertension 2002;39:919–22.
[207] Gardemann A, Lohre J, Cayci S, Katz N, Tillmans H, Haberbosch W. The T allele of the missense Glu(298)Asp endothelial nitric oxide synthase gene polymorphism is associated with coronary heart disease in younger individuals with high atherosclerotic risk profile. Atherosclerosis 2002;160:167–75.
[208] Veldman BA, Spiering W, Doevendans PA. The Glu298Asp polymorphism of the NOS 3 gene as a determinant of the baseline production of nitric oxide. J Hypertens 2002;20:2023–7.
[209] Tesauro M, Thompson WC, Rogliani P, Qi L, Chaudhari PP, Moss J. Intracellular processing of endothelial nitric oxide synthase isoforms associated with differences in severity of cardiopulmonary diseases: cleavage of proteins with aspartate vs. glutamate at position 298. Proc Natl Acad Sci USA 2000;97:2832–5.
[210] Williams IL, Wheatcroft SB, Shah AM, Kearney MT. Obesity, atherosclerosis and the vascular endothelium: mechanisms of reduced nitric oxide bioavailability in humans. Int J Obesity 2002;26: 754–64.
[211] Anderson RA, Jones CJ, Goodfellow J. Is the fatty meal a trigger for acute coronary syndromes. Atherosclerosis 2001;159:9–15.
[212] Lane DA, Grant PJ. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. Blood 2000;95:1517–32.
[213] Franco RF, Reitsma PH. Gene polymorphisms of the haemostatic system and the risk of arterial thrombotic disease. Br J Haematol 2001;115:491–506.
[214] Iacoviello L, Vischetti M, Zito F, Benedetta Donati M. Genes encoding fibrinogen and cardiovascular risk. Hypertension 2001;38: 1199–1203.
[215] Hoffstedt J, Andersson IL, Persson L, Isaksson B, Arner P. The common–675 4G/5G polymorphism in the plasminogen activator inhibitor–1 gene is strongly associated with obesity. Diabetologia 2002;45:584–7.
[216] Townend J, O'Sullivan J, Wilde JT. Hyperhomocysteinaemia and vascular disease. Blood Reviews 1998;12:23–34.
[217] Kluijtmans LAJ, Kastelein JJP, Lindemans J, Boers GH, Heil SG, Bruschke AV, Jukema JV, van der Heuvel LP, Trijbels FJ, Boerma GJ, Verheugt FW, Willems F, Blom HJ. Thermolabile methylenetetrahydrofolate reductase in coronary artery disease. Circulation 1997; 96:2573–7.
[218] Gudnason V, Stansbie D, Scott J, Bowron A, Nicaud V, Humphries S. C677T (thermolabile alanine/valine) polymorphism in methylenetetrahydrofolate reductase (MTHFR): its frequency and impact on plasma homocysteine concentration in different European populations: EARS group. Atherosclerosis 1998;136:347–54.
[219] Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJH, den Heijer M, Kluijtmans LAJ, van der Heuvel LP, Rozen R. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nature Genet 1995;10:111–3.
[220] Weisberg IS, Jacques PF, Selhub J, Bostom AG, Chen Z, Curtis Ellison R, Eckfeldt JH, Rozen R. The 1298A→C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with homocysteine. Atherosclerosis 2001;156:409–15.

[221] Meisel C, Cascorbi I, Gerloff T, Stangl V, Laule M, Muller JM, Wernecke KD, Baumann G, Roots I, Stangl K. Identification of six methylenetetrahydrofolate reductase (MTHFR) genotypes resulting from common polymorphisms: impact on plasma homocysteine levels and development of coronary artery disease. Atherosclerosis 2001;154:651–8.

[222] Watkins D, Ru M, Hwang HY, Kim CD, Murray A, Philip NS, Kim W, Legakis H, Wai T, Hilton JF, Ge B, Dore C, Hosack A, Wilson A, Gravel RA, Shane B, Hudson TJ, Rosenblatt DS. Hyperhomocysteinemia due to methionine synthase deficiency, cblG: structure of the MTR gene, genotype diversity, and recognition of a common mutation, P1173L. Am J Hum Genet 2002;71:143–53.

[223] Gaughan DJ, Kluijtmans LA, Barbaux S, McMaster D, Young IS, Yarnell JW, Evans A, Whitehead AS. The methionine synthase reductase (MTRR) A66G polymorphism is a novel genetic determinant of plasma homocysteine concentrations. Atherosclerosis 2001; 157:451–6.

[224] De Stefano V, Dekou V, Nicaud V, Chasse JF, London J, Stansbie D, Humphries SE, Gudnason V. Linkage disequilibrium at the cystathionine beta synthase (CBS) locus and the association between genetic variation at the CBS locus and plasma levels of homocysteine. Ann Hum Genet 1998;62:481–90.

[225] Devlin AM, Ling EH, Peerson JM, Fernando S, Clarke R, Smith AD, Halsted CH. Glutamate carboxypeptidase II: a polymorphism associated with lower levels of serum folate and hyperhomocysteinemia. Hum Mol Genet 2000;22:2837–44.

[226] Lievers KJA, Kluijtmans LAJ, Boers GHJ, Verhoef P, den Heijer M, Trijbels FJ, Blom HJ. Influence of a glutamate carboxypeptidase II (GCPII) polymorphism (1561C→T) on plasma homocysteine, folate and vitamin B(12) levels and its relationship to cardiovascular disease risk. Atherosclerosis 2002;164:269–73.

[227] Trinh BN, Ong CN, Coetzee GA, Yu MC, Laird PW. Thymidylate synthase: a novel genetic determinant of plasma homocysteine and folate levels. Hum Genet 2002;111:299–302.

[228] Namour F, Olivier J, Abdelmouttaleb I, Adjalla C, Debard R, Salvat C, Gueant J. Transcobalamin codon 259 polymorphism in HT-29 and Caco-2 cells and in Caucasians: relation to transcobalamin and homocysteine concentration in blood. Blood 2001;97:1092–8.

[229] Vineis P, Malats N, Lang M, d'Errico A, Caporaso N, Cuzick J, Boffetta P. Metabolic Polymorphisms and Susceptibility to Cancer. IARC Sci Publ148. Lyon: IARC, 2000.

[230] Sugimura T. Nutrition and dietary carcinogens. Carcinogenesis 2000;21:387–95.

[231] Bartsch H, Nair U, Risch A, Rojas M, Wilkman H, Alexandrov K. Genetic polymorphisms of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomark Prev 2000;9:3–28.

[232] Houlston RS, Tomlinson IP. Polymorphisms and colorectal tumor risk. Gastroenterology 2001;121:282–301.

[233] Hein DW, Doll MA, Fretland AJ, Leff MA, Webb SJ, Xiao GH, Devanaboyina US, Nangju NA, Feng Y. Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms. Cancer Epidemiol Biomark Prev 2000;9:29–42.

[234] Cotton SC, Sharp L, Little J, Brockton N. Glutathione S-transferase polymorphisms and colorectal cancer: a HuGE review. Am J Epidemiol 2000;151:7–32.

[235] Strange RC, Spiteri MA, Ramachandran S, Fryer AA. Glutathione-S-transferase family of enzymes. Mutat Res 2001;482:21–6.

[236] Nebert DW, Roe AL, Vandale SE, Bingham E, Oakley GG. NAD(P)H:quinone oxidoreductase (NQO1) polymorphism, exposure to benzene, and predisposition to disease: a HuGE review. Genet Med 2002;4:62–70.

[237] Lee WJ, Brennan P, Boffetta P, London SJ, Benhamou S, Rannug A, To-Figueras J, Ingelman-Sundberg M, Shields P, Gaspari L, Taioli E. Microsomal epoxide hydrolase polymorphisms and lung cancer risk: a quantitative review. Biomarkers 2002;7:230–41.

[238] Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, Kim CH, Park JH, Kam S, Kim IS, Jung TH. Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. Cancer Epidemiol Biomark Prev 2002;11:23–7.

[239] Nelson HH, Kelsey KT, Mott LA, Karagas MR. The XRCC1 Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer: evidence of gene-environment interaction. Cancer Res 2002;62: 152–5.

[240] Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. A population-based study of the Arg399Gln polymorphism in X-ray repair cross-complementing group 1 (XRCC1) and risk of pancreatic carcinoma. Cancer Res 2002;62:4630–6.

[241] Matullo G, Guarrera S, Carturan S, Peluso M, Malaveille C, Davico L, Piazza A, Vineis P. DNA repair gene polymorphisms, bulky DNA adducts in white cells and bladder cancer in a case-control study. Int J Cancer 2001;92:562–7.

[242] Stern MC, Umbach DM, Lunn RM, Taylor JA. DNA repair gene XRCC3 codon 241 polymorphism, its interaction with smoking and XRCC1 polymorphisms, and bladder cancer risk. Cancer Epidemiol Biomark Prev 2002;11:939–43.

[243] Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M, Harris CC. Genetic polymorphisms in DNA repair genes and risk of lung cancer. Carcinogenesis 2001;22:593–7.

[244] Vogel U, Hedayati M, Dybdahl M, Grossman L, Nexo BA. Polymorphisms of the DNA repair gene XPD: correlations with risk of basal cell carcinoma revisited. Carcinogenesis 2001;22:899–904.

[245] Zhou W, Liu G, Miller DP, Thurston SW, Xu LL, Wain JC, Lynch TJ, Su L, Christiani DC. Gene-environment interaction for the ERCC2 polymorphisms and cumulative cigarette smoking exposure in lung cancer. Cancer Res 2002;62:1377–81.

[246] Le Marchand L, Donlon T, Lum-Jones A, Seifried A, Wilkens LR. Association of the hOGG1 Ser326Cys polymorphism with lung cancer risk. Cancer Epidemiol Biomark Prev 2002;11:409–12.

[247] Xu J, Zheng SL, Turner A, Isaaks SD, Wiley KE, Hawkins GA, Chang BL, Bleecker ER, Walsh PC, Meyers DA, Isaaks WB. Associations between hOGG1 sequence variants and prostate cancer susceptibility. Cancer Res 2002;62:2253–7.

[248] Kaur TB, Travaline JM, Gaughan JP, Richie JP, Stellman SD, Lazarus P. Role of polymorphisms in codons 143 and 160 of the O^6-alkylguanine DNA alkyltransferase gene in lung cancer risk. Cancer Epidemiol Biomark Prev 2000;9:339–42.

[249] Shen H, Wang L, Spitz MR, Hong WK, Mao L, Wei Q. A novel polymorphism in human cytosine DNA-methyltransferase-3B promoter is associated with an increased risk of lung cancer. Cancer Res 2002;62:4992–5.

[250] Zheng Y, Shen H, Sturgis EM, Wang LE, Eicher SA, Strom SS, Frazier ML, Spitz MR, Wei Q. Cyclin D1 polymorphism and risk for squamous cell carcinoma of the head and neck: a case-control study. Carcinogenesis 2001;22:1195–9.

[251] Simpson DJ, Fryer AA, Grossman AB, Wass JA, Pfeifer M, Kros JM, Clayton RN, Farrell WE. Cyclin D1 (CCND1) genotype is associated with tumour grade in sporadic pituitary adenomas. Carcinogenesis 2001;22:1801–7.

[252] Wang L, Habuchi T, Takahashi T, Mitsumori K, Kamoto T, Kakehi Y, Kakinuma H, Sato K, Nakamura A, Ogawa O, Kato T. Cyclin D1 gene polymorphism is associated with an increased risk of urinary bladder cancer. Carcinogenesis 2002;23:257–64.

[253] Ralhan R, Agarwal S, Mathur M, Wasylyk B, Srivastava A. Association between polymorphism in p21(Waf1/Cip1) cyclin-dependent kinase inhibitor gene and human oral cancer. Clin Cancer Res 2000;6:2440–7.

[254] Jupe ER, Badgett AA, Neas BR, Craft MA, Mitchell DS, Resta R, Mulvihill JJ, Aston CE, Thompson LF. Single nucleotide polymorphism in prohibitin 39 untranslated region and breast cancer susceptibility. Lancet 2001;357:1588–9.

[255] Dunning AM, Healey CS, Pharoah PD, Teare MD, Ponder BA, Easton DF. A systematic review of genetic polymorphisms and breast cancer risk. Cancer Epidemiol Biomark Prev 1999;8:843–54.
[256] Nwosu V, Carpten J, Trent JM, Sheridan R. Heterogeneity of genetic alterations in prostate cancer: evidence of the complex nature of the disease. Hum Mol Genet 2001;10:2313–8.
[257] Adlercreutz H. Phyto-oestrogens and cancer. Lancet Oncol 2002;3: 364–73.
[258] Friso S, Choi S-W. Gene-nutrient interactions and DNA methylation. J Nutr 2002;132:2382S–7S.
[259] Friso S, Choi S-W, Girelli D, Mason JB, Dolnikowski GG, Bagley PJ, Olivieri O, Jacques PF, Rosenberg IH, Corrocher R, Selhub J. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. Proc Natl Acad Sci USA 2002;99:5606–11.
[260] Giovannucci E. Epidemiologic studies of folate and colorectal neoplasia: a review. J Nutr 2002;132:2350S–5S.
[261] Chen J, Ma J, Stampfer MJ, Palomeque C, Selhub J, Hunter DJ. Linkage disequilibrium between the 677C>T and 1298A>C polymorphisms in human methylenetetrahydrofolate reductase gene and their contributions to risk of colorectal cancer. Pharmacogenetics 2002;12:339–42.
[262] Kimura F, Franke KH, Steinhoff C, Golka K, Roemer HC, Anastasiadis AG, Schulz WA. Methyl group metabolism gene polymorphisms and susceptibility to prostatic carcinoma. Prostate 2000;45: 225–31.
[263] Song C, Xing D, Tan W, Wei Q, Lin D. Methylenetetrahydrofolate reductase polymorphisms increase risk of esophageal squamous cell carcinoma in a Chinese population. Cancer Res 2001;61:3272–5.
[264] Skibola CF, Smith MT, Kane E, Roman E, Rollinson S, Cartwright RA, Morgan G. Polymorphisms in methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults. Proc Natl Acad Sci USA 1999;96:12810–5.
[265] Ma J, Stampher MJ, Christensen B, Giovanucci E, Hunter DJ, Chen J, Willett WC, Selhub J, Hennekens CH, Gravel R, Rozen R. A polymorphism of the methionine synthase gene: association with plasma folate, vitamin B12, homocyst(e)ine, and colorectal cancer risk. Cancer Epidemiol Biomark Prev 1999;8:825–9.
[266] Skibola CF, Smith MT, Hubbard A, Shane B, Roberts AC, Law GR, Rollinson S, Roman E, Cartwright RA, Morgan GJ. Polymorphisms in the thymidylate synthase and serine hydroxymethyltransferase gene and risk of adult acute lymphocytic leukemia. Blood 2002;99: 3786–91.
[267] Shannon B, Gnanasampanthan S, Beilby J, Iacopetta B. A polymorphism in the methylenetetrahydrofolate reductase gene predisposes to colorectal cancers with microsatellite instability. Gut 2002;50: 520–4.
[268] Krajinovic M, Costea I, Chiasson S. Polymorphism of the thymidylate synthase gene and outcome of acute lymphoblastic leukaemia. Lancet 2002;359:1033–4.
[269] Ulrich CM, Bigler J, Bostick R, Fosdick L, Potter JD. Thymidylate synthase promoter polymorphism, interaction with folate intake, and risk of colorectal adenomas. Cancer Res 2002;62:3361–4.
[270] Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353–64.
[271] Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249–57.
[272] Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegland SJ, Holash J. Vascular-specific growth factors and blood vessel formation. Nature 2000;407:242–8.
[273] Howell WM, Bateman AC, Turner SJ, Collins A, Theaker JM. Influence of vascular endothelial growth factor single nucleotide polymorphisms on tumour development in cutaneous malignant melanoma. Genes Immun 2002;3:229–32.
[274] McCarron SL, Edwards S, Evans PR, Gibbs R, Dearnley DP, Dowe A, Southgate C, Easton DF, Eeles RA, Howell WM. Influence of cytokine gene polymorphisms on the development of prostate cancer. Cancer Res 2002;62:3369–72.
[275] Ward EG, Grosios K, Markham AF, Jones PF. Genomic structures of the human angiopoietins show polymorphism in angiopoietin-2. Cytogenet Cell Genet 2001;94:147–54.
[276] Tsukasaki K, Miller CW, Kubota T, Takeuchi S, Fujimoto T, Ikeda S, Tomonaga M, Koeffler HP. Tumor necrosis factor alpha polymorphism associated with increased susceptibility to development of adult T-cell leukemia/lymphoma in human T-lymphotropic virus type 1 carriers. Cancer Res 2001;61:3770–4.
[277] Ziv E, Cauley J, Morin PA, Saiz R, Browner WS. Association between the T29→C polymorphism in the transforming growth factor beta 1 gene and breast cancer among elderly white women: the study of osteoporotic fractures. JAMA 2001;285:2859–63.
[278] Barber MD, Powell JJ, Lynch SF, Fearon KC, Ross JA. A polymorphism in the interleukin-1 beta gene influences survival in pancreatic cancer. Br J Cancer 2000;83:1443–7.
[279] Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, Amorim A, Seruca R, Caldas C, Carneiro F, Sobrinho-Simoes M. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. Gastroenterology 2001;121:823–9.
[280] Cheon KT, Choi KH, Lee HB, Park SK, Rhee YK, Lee YC. Gene polymorphisms of endothelial nitric oxide synthase and angiotensin-converting enzyme in patients with lung cancer. Lung 2000;178: 351–60.
[281] Medeiros R, Morais A, Vasconcelos A, Costa S, Pinto D, Oliveira J, Lopes C. Endothelial nitric oxide synthase gene polymorphism and genetic susceptibility to prostate cancer. Eur J Cancer Prev 2002; 11:343–50.
[282] Hefler LA, Ludwig E, Lampe D, Zeillinger R, Leodolter S, Gitsch G, Koelbl H, Tempfer CB. Polymorphisms of the endothelial nitric oxide synthase gene in ovarian cancer. Gynecol Oncol 2002;86: 134–7.
[283] Loktionov A, Watson MA, Stebbings WSL, Speakman CTM, Bingham SA. Plasminogen activator inhibitor-1 gene polymorphism and colorectal cancer risk and prognosis. Cancer Lett 2003;189:189–96.
[284] Moysich KB, Freudenheim JL, Baker JA, Ambrosone CB, Bowman ED, Schisterman EF, Vena JE, Shields PG. Apolipoprotein E genetic polymorphism, serum lipoproteins, and breast cancer risk. Mol Carcinogenesis 2000;27:2–9.
[285] Watson MA, Gay L, Stebbings WSL, Speakman CTM, Bingham SA, Loktionov A. Apolipoprotein E gene polymorphism and colorectal cancer: gender-specific modulation of risk and prognosis. Clin Science 2003;104 (in press).
[286] Cao Y, Cao R, Brakenhielm E. Antiangiogenic mechanisms of diet-derived polyphenols. J Nutr Biochem 2002;13:380–90.
[287] Fotsis T, Pepper M, Adlercreutz H, Fleischmann G, Hase T, Montesano R, Schweigerer L. Genistein, a dietary-derived inhibitor of in vitro angiogenesis. Proc Natl Acad Sci USA 1993;90:2690–4.
[288] Rose DP, Connoly JM. Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. Nutr Cancer 2000;37:119–27.
[289] James SJ, Muskhelishvili L, Gaylor DW, Turturro A, Hart R. Up-regulation of apoptosis with dietary restriction: implications for carcinogenesis and aging. Environ Health Perspect 1998;106(Suppl 1):307–12.
[290] Huang XE, Hamajima N, Saito T, Matsuo K, Mizutani M, Iwata H, Iwase T, Miura S, Mizuno T, Tokudome S, Tajima K. Possible association of beta2- and beta3-adrenergic receptor gene polymorphisms to breast cancer. Breast Cancer Res 2001;3:264–9.
[291] Takezaki T, Hamajima N, Matsuo K, Tanaka R, Hirai T, Kato T, Ohashi K, Tajima K. Association of polymorphisms in the beta-2 and beta-3 adrenoceptor genes with risk of colorectal cancer in Japanese. Int J Clin Oncol 2001;6:117–22.
[292] Smith WM, Zhou XP, Kurose K, Gao X, Latif F, Kroll T, Sugano K, Cannistra SA, Clinton SK, Maher ER, Prior TW, Eng C. Opposite association of two PPARG variants with cancer: overrepresentation

of H449H in endometrial carcinoma cases and underrepresentation of P12A in renal cell carcinoma cases. Hum Genet 2001;109:146–51.
[293] Tisdale MJ. Cachexia in cancer patients. Nature Reviews (Cancer) 2002;2:862–71.
[294] Laviano A, Russo M, Freda F, Rossi-Fanelli F. Neurochemical mechanisms for cancer anorexia. Nutrition 2002;18:100–5.
[295] Willett WC. Balancing life-style and genomics research for disease prevention. Science 2002;296:695–8.
[296] Miller RD, Kwok PY. The birth and death of human single-nucleotide polymorphisms: new experimental evidence and implications for human history and medicine. Hum Mol Genet 2001;10:2195–8.
[297] Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: practical considerations. Nature Reviews (Genetics) 2002;3:391–6.
[298] Ardlie KG, Krugliak L, Seielstad M. Patterns of linkage disequilibrium in the human genome. Nature Reviews (Genetics) 2002;3:299–309.