How Diet Interacts with Longevity Genes

Diyet Longevity Genleriyle Nasıl Etkileşir?

Ali SAZCI[a]

[a]Tıbbi Biyoloji AD,
Kocaeli Üniversitesi Tıp Fakültesi,
KOCAELİ

Yazışma Adresi/*Correspondence:*
Ali SAZCI
Kocaeli Üniversitesi Tıp Fakültesi,
Tıbbi Biyoloji AD,
Umuttepe, 41380, KOCAELİ
alisazci@gmail.com

ABSTRACT Both men and women share most genetic information, however they have significantly different disease susceptibilities. Gender influences the risk of nearly all common diseases affecting both men and women, such as atherosclerosis, hypetension, diabetes and their preceding risk factors for example, hyperlipidemia, insulin resistance, and obesity. The aim of this article was to present the interplay between genes, gender, and disease susceptibility, and also assess it in the context of the complexity of environmental factors in terms of balance between health and disease. In conclusion, gender-specific differences in morbidity and mortality may be mediated in part by genetic factors and by their differential response to the environment. In this regard, data produced will result in an ability to provide personalized nutritional recommendations to prevent chronic disorders in the future.

Key Words: Gender, nutrigenetics, nutrigenomics, obesity, cardiovascular disease,diet

ÖZET Kadın ve erkek genetik bilginin çoğunu paylaşmasına rağmen, hastalıklara olan yatkınlığı oldukça farklıdır. Seks, erkek ve kadını etkileyen hemen hemen tüm ortak hastalık risklerini etkilemektedir, örneğin aterosklerosis, hipertansiyon, diyabet ve bunları oluşturan risk faktörleri örneğin, hiperlipidemi, insülin direnci, ve obesite gibi. Bu makalenin amacı gen, seks ve hastalık hassasiyeti arasındaki ilişkiyi kurarak, ve ayrıca bunları çevresel faktörlerin komplekisliği içerisinde değerlendirerek hastalık ve sağlık arasındaki dengeyi kurmaktır. Sonuç olarak, bir hastalığın sıklık derecesi ve bundan oluşan kayıplarda ki sekse bağlı farklılıklar genetik faktörler tarafından ve onların çevreye farklı cevaplarından kaynaklanmaktadır. Bu bağlamda, gelecekte kronik hastalıklardan korunmada kişisel besinlerin belirlenmesinde bu konuda üretilen bilgiler önemli rol oynayacaktır.

Anahtar Kelimeler: Seks, besingenetiği, besingenomiksi, obesite, kardiyovasküler hastalık, diyet

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Nutritional genomics is a branch of science studying the interplay between human genome, nutrition and health. It can be explained in two sections: Nutrigenomics is the study of the effect of nutrients on health through altering genome, proteome, metabolome and the resulting changes in physiology. Nutrigenetics is the study of the effect of genetic variations on the interaction between diet and health with implications to disease susceptibility.[1-3]

As we know today, stem cells can be differantiated into any type of tissue based on what vitamins and bioactive components of nutrition we take in are available.

One of the results of the human genome Project is that some genes known to be associated with human diseases result in monogenic diseases, that is, a mutation in one gene is sufficient to cause the disease. In some cases, modifying the dietary intake can prevet some monogenic diseases. One example is phenylketonuria, a genetic disease characterized by defective phenylalanine hydroxylase enzyme. Phenylalanine-restricted tyrosine-supplemented diets are a means to nutritionally treat this monogenic disease.[4]

On the other hand, many common diseases, such as obesity, cancer, diabetes, and cardiovascular disease, are polygenic diseases, that is, they arise from the dysfunction in a number of genes involved in some biological pathways. Dietary intervention to prevent such diseases is complex and an ambitious goal. In this regard, variations in MTHFR, ACE, APOE, PON, and PPAR-γ candidate genes for longevity are known to be associated with human multifactorial disorders.[5]

A number of variations in genes have been shown to increase the susceptibility to diet-related diseases. These variations have been associated with Type 2 diabetes mellitus, hypertension, obesity, cardiovascular diseases, some autoimmune diseases and cancers. Nutrigenetics aims to study such susceptibility genes and provides dietary interventions for individuals at risk of such diseases.

As it has been shown in model organisms. The common variants in several genes in the insulin/IGF1 pathway are associated with human lifespan.[6]

Hypertriglyceridemia, a strong predictor of atherogenic cardiovascular disease (CVD) is the result of increased plasma concentration of very low density lipoprotein(VLDL). Elevated VLDL and hypertriglyceridemia reduce the high-density lipoprotein(HDL) level by generating small, dense low-density lipoprotein(LDL). Grape seed proanthocyanidins downregulate the expression of SREBP1, DGAT2 and MTP genes, thus resulting in the lower plasma levels of VLDL and TG. LDL cholesterol has a causal role in the development of cardiovascular disease. Variation in LDL cholesterol concentrations reveals a polygenic trait.[7]

Two missense mutations in exons coding the aminoterminal transcriptional activating domain of SREBP-1 gene were associated with severe insulin resistance. Another association was found between an intronic single nucleotide polymorphism (C/T) between exons 18 and 19 and the onset of diabetes in men, but not in women. These mutations in SREBP-1 gene may increase the sensitivity to developing diabetes.[7]

Moreover, the SREBP-1 appears to be susceptible to diet, and thus it can be a target for nutritional intervention. Studies in mice have shown that SREBP-1 mRNA expression was highly induced in mice having one polymorphism (–468 A/G) after the consumption of high fructose diets, thus implying that a polymorphism can also modulate the sensitivity of a gene to dietary intervention.[7]

Hyperlipidemia is usually known to be associated with atherosclerosis and coronary heart disease. Therapy includes lifestyle changes as alterations in the patient's diet, physical activity and treatment with pharmaceuticals such as statins. However, individuals respond differently to the treatment. This was attributed to genetic variations within the population. Genetic variations in genes encoding for apolipoproteins, can alter individual sensitivity to developing cardiovascular diseases. Individuals with the E4 allele in the apolipoprotein E gene show higher low-density lipoprotein-cholesterol levels with increased dietary fat intake compared with those with the other (E2, E3) alleles receiving equivalent amounts of dietary fat.

One polymorphism (-75 G/A) in the apolipoprotein A1 gene in women is associated with an increase in HDL-cholesterol levels with the increase in the dietary intake of polyunsaturated fatty acids (PUFA). Individuals with the A variant showed an increase in the protective HDL levels following an increased consumption of PUFA compared with those with the G variant taking similar amounts of PUFA.

One polymorphism (-514 CC) in the hepatic lipase gene is associated with an increase in protective HDL levels compared with the TT genotype (common in African-Americans) in response to high fat diet.

In a genome-wide association study, two SNPs (rs599839, rs4970834) showed statistical association with LDL cholestrol at chromosomal locus 1p13.3.[8]

Physical exercise and dietary measures are currently the only known ways of slowing the aging process.

Genetic variation within the FOXO3A gene was strongly associated with human longevity.[9-11] The human forkhead box O3A gene (FOXO3A) encodes an evolutionarily conserved key regulator of the insulin–IGF1 signaling pathway that is known to influence metabolism and lifespan in model organisms. A recent study described 3 SNPs(rs2764264, rs13217795, rs2802292) in the

FOXO3A gene that were statistically significantly associated with longevity in a discovery sample of long-lived men of Japanese ancestry inhabiting in Hawaii.[11] This finding was replicated in two independent populations including German, and Italian. The analysis in the French centenarian sample generated a trend in line with the Japanese and German collections, however did not produce a statistically significant result. However the analysis of Dutch centenarian sample did not yield a statistically significant data. German group also showed an association between an SNP(rs2802288) in the FOXO3A gene and longevity.[10] In japanese and italian centenarians , the association of SNPs in the FOXO3A gene were only studied in male but not female centenarians. However Flachsbart et al extended the initial finding observed in Japanese men to women and indicates that both genders were likely to be equally affected by variation in FOXO3A gene. Replication in a French centenarian sample generated a trend that supported the previous results.

The FOXO3A genotype was significantly associated with plasma insulin levels, CHD, cancer , and Type2 diabetes prevalence. The FOXO protein acts as a mediator of the effects of insulin and insulin-like growth factors on diverse physiological functions, including cell proliferation,apoptosis, and metabolism, are the targets of protein kinases, influence cell cycle progression, and regulate resistance to oxidative stres in vitro. Moreover in vivo, the FOXO protein modifies hepatic glucose output in response to insulin and mediates other metabolic actions. Therefore FOXO proteins may modulate insulin effects on metabolism and influence longevity in humans. The FOXO3A gene may influence human aging through interfering with oxidative stress. In C.elegans, the DAF-16 gene upregulates the expression of manganese superoxide dismutase (SOD2) that ptrotects cells from the effect of superoxide by converting superoxide to hydrogen peroxide. In humans the FOXO3A proteins may be doing the same thing. In vivo studies reveal that oxidative lesions in DNA, proteins and other tissues accumulate with age and calorically restricted diets reduce this damage.[14-16] Insulin levels in both cases and controls were lower in the GG genotypes of the FOXO3A gene in japanese male.

In conclusion, this is a new study field. Thus there are little data available to make definite conlusions. As the data accumulate, we will beter understand the interplay between genes and the diet in the future and make sound recommendations for individualized personal treatment.

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