

**Nutrigenetik:
Kişisel Beslenme
Bilimini Uygulamak**



© Copyright 2023

Bu kitabın, basım, yayın ve satış hakları Akademisyen Kitabevi A.Ş.'ne aittir. Anılan kuruluşun izni alınmadan kitabın tümü ya da bölümleri mekanik, elektronik, fotokopi, manyetik kağıt ve/veya başka yöntemlerle çoğaltılamaz, basılamaz, dağıtılamaz. Tablo, şekil ve grafikler izin alınmadan, ticari amaçlı kullanılamaz. Bu kitap T.C. Kültür Bakanlığı bandrolü ile satılmaktadır.

Orjinal ISBN	ISBN
978-0-12-385900-6	978-625-399-006-0
Orjinal Kitap Adı	Kitap Adı
Nutrigenetics Applying the Science of Personal Nutrition	Nutrigenetik: Kişisel Beslenme Bilimini Uygulamak
Orjinal Editör	Çeviri Editörleri
Martin Kohlmeier	Prof. Dr. Murat BAŞ ORCID iD: 0000-0002-0494-301X Doç. Dr. K. Esen KARACA ÇELİK ORCID iD: 0000-0002-3625-4761
Yayın Koordinatörü	Baskı ve Cilt
Yasin DİLMEN	Vadi Matbaacılık
Sayfa ve Kapak Tasarımı	Bisac Code
Akademisyen Dizgi Ünitesi	HEA017000
Yayıncı Sertifika No	DOI
47518	10.37609/akya.1963

UYARI

Bu üründe yer alan bilgiler kaynak olarak sunulmuştur. Herhangi bir konuda profesyonel tıbbi danışmanlık veya tıbbi tanı amacıyla kullanılmamalıdır. Akademisyen Kitabevi ve alıcı arasında herhangi bir şekilde doktor-hasta, terapist-hasta ve/veya başka bir sağlık sunum hizmeti ilişkisi oluşturmaz. Bu ürün profesyonel tıbbi kararların eşleniği veya yedeği değildir. Akademisyen Kitabevi ve bağlı şirketleri, yazarları, katılımcıları, partnerleri ve sponsorları ürün bilgilerine dayalı olarak yapılan bütün uygulamalardan doğan, insanlarda ve cihazlarda yaralanma ve/veya hasarlardan sorumlu değildir.

İlaçların veya başka kimyasalların reçete edildiği durumlarda, tavsiye edilen dozunu, ilacın uygulanacak süresi, yöntemi ve kontraendikasyonlarını belirlemek için, okuyucuya üretici tarafından her ilaca dair sunulan güncel ürün bilgisini kontrol etmesi tavsiye edilmektedir. Dozun ve hasta için en uygun tedavinin belirlenmesi, tedavi eden hekimin hastaya dair bilgi ve tecrübelerine dayanak oluşturması, hekimin kendi sorumluluğundadır.

Akademisyen Kitabevi, üçüncü bir taraf tarafından yapılan ürüne dair değişiklikler, tekrar paketlemeler ve özelleştirmelerden sorumlu değildir.

GENEL DAĞITIM

Akademisyen Kitabevi A.Ş.

Halk Sokak 5 / A Yenışehir / Ankara

Tel: 0312 431 16 33

siparis@akademisyen.com

www.akademisyen.com

Nutrigenetik: Kişisel Beslenme Bilimini Uygulamak

ÇEVİRİ EDITÖRLERİ

Prof. Dr. Murat BAŞ - Acıbadem Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, İstanbul.

Doç. Dr. K. Esen KARACA ÇELİK - İzmir Demokrasi Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, İzmir.

ÇEVİRENLER

Öğr. Gör. Merve İNCE PALAMUTOĞLU - Afyonkarahisar Sağlık Bilimleri Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, Afyonkarahisar.

Öğr. Gör. Simge SİPAHİ - Acıbadem Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, İstanbul.

Arş. Gör. Bartu Eren GÜNEŞLİOL - Gazi Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, Ankara.

Uzm. Dyt. İpek AĞACA ÖZGER – Renkli Diyet, İstanbul.

Önsöz

Beslenme hakkındaki düşüncelerimizi, besin öğelerinin genlerle nasıl etkileşime girdiğini inceleyen nutrigenetik alandan daha fazla hiçbir şey değiştiremez. Bu alanın önemi anlaşılmaya başlamadan önce, beslenme araştırmalarının sonuçları genellikle kafa karıştırıcıydı. Tüm insanların metabolik olarak benzer olduğunu düşündük ve bir besin öğesine tepkilerini incelediğimizde, yanıt verenleri ve yanıt vermeyenleri bulduğumuzda, bu varyasyonu çalışmanın bilimsel tasarımındaki zayıflıklara bağladık. Haber makaleleri, sırf bir araştırma çalışması sonraki hafta tam tersi bir sonuç bulsun diye, önceki haftadan yeni bir keşif duyuruyordu. Halkın, sağlığını iyileştirmek için bu bilgilere göre hareket etmesi zordu.

Şimdi, genetik ve epigenetik kodlamada farklılıklar olduğu için insanların metabolik olarak çok farklı olabileceğini biliyoruz ve araştırmacıların neden bazı insanların bir besin öğesine tepki verirken diğerlerine vermediğini gözlemlediğini açıklıyoruz. Modern genetik yöntemleri kullanarak, yanıt verenlerin kim olacağını doğru bir şekilde tahmin etmek çoğu zaman mümkündür. Bilim insanları şu anda besin öğelerine olan gereksinimleri ve tepkileri öngören kapsamlı bir gen-besin öğesi etkileşimleri kataloğu geliştiriyorlar. Bugün gen-besin öğesi etkileşimlerinin yüzlercesi biliniyor ama yakında on binlercesi tespit edilecek ve bu katalog optimal besin öğesi alımı için bireyselleştirilmiş tavsiyeler geliştirmenin temeli olacak. Beş ile on yıl içinde, doktorların, hemşirelerin ve diyetisyenlerin klinik uygulamalarını değiştirmek için bu nutrigenetik kataloğu kullanacaklarından eminim.

Genetik, epigenetik ve beslenme karmaşık bilimsel alanlardır ve özelleştirilmiş beslenme müdahaleleri geliştirmek için nutrigenetiği kullanmaya hazır olmak isteyen kişilerin çok sayıda yeni bilgiye hakim olmaları gerekir.

Dr. Kohlmeier'in kitabı bu öğrenme macerasına başlamak için mükemmel bir yer.

Steven H. Zeisel MD, PhD

Kenan Distinguished Üniversitesi Beslenme ve Pediatri Profesörü Chapel Hill'deki
Kuzey Karolina Üniversitesi UNC Beslenme Araştırma Enstitüsü Direktörü 500

Laureate Way Kannapolis, NC 28081

5 Temmuz 2012

İçindekiler

Giriş	v
BÖLÜM 1. Genotip Temelli Beslenme Kararları İçin Zaman Geldi mi?	1
Merve İNCE PALAMUTOĞLU	
BÖLÜM 2. Genetik Geçiş Nasıl Çalışır?	17
Merve İNCE PALAMUTOĞLU	
BÖLÜM 3. Nutrigenetik Farklılıklar Nereden Gelmektedir?	57
Merve İNCE PALAMUTOĞLU	
BÖLÜM 4. Besin Öğeleri Genetikten Nasıl Etkilenir?	103
Simge SİPAHİ, Bartu Eren GÜNEŞLİOL	
BÖLÜM 5. Nutrigenetik Uzun Süreli Sağlığı Nasıl Etkiler?	223
İpek AĞACA ÖZGER	
BÖLÜM 6. Son Bulguların Ne Anlama Geldiğini Nasıl Bilebiliriz?	273
İpek AĞACA ÖZGER	
BÖLÜM 7. Nutrigenetiğin Pratik Kullanımları	307
Bartu Eren GÜNEŞLİOL	
BÖLÜM 8. Genetik Bilgiyi Güvende Tutmak	335
Bartu Eren GÜNEŞLİOL	
GENOM SÖZLÜĞÜ	355
Bartu Eren GÜNEŞLİOL	
KAYNAKLAR	365
İNDEKS	369

Kaynaklar

365

NUTRİGENETİK İLE İLGİLİ BİLİM DERGİLERİ

American Journal of Clinical Nutrition, <http://www.ajcn.org/>
American Journal of Human Genetics, <http://www.cell.com/AJHG/>
British Journal of Nutrition, <http://journals.cambridge.org/action/displayJournal?jid¼bjn>
Drug Metabolism and Predisposition, <http://dmd.aspetjournals.org/>
European Journal of Clinical Nutrition, <http://www.nature.com/ejcn/index.html>
Genes and Nutrition, <http://www.springer.com/biomed/human+genetics/journal/12263>
Journal of Nutrigenetics and Nutrigenomics, <http://content.karger.com/ProdukteDB/produkte.asp?Aktion¼JournalHome&ProduktNr¼232009>
Journal of Nutrition, <http://jn.nutrition.org/>
Molecular Genetics and Metabolism, <http://www.sciencedirect.com/science/journal/10967192>
Molecular Nutrition & Food Research, <http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291613e4133>
Nature Genetics, <http://www.nature.com/ng/journal/vaop/ncurrent/index.html>
PLoS Genetics, <http://www.plosgenetics.org/home.action>
Public Health Genomics, <http://content.karger.com/ProdukteDB/produkte.asp?issn¼1662e8063>
The Pharmacogenomics Journal, <http://www.nature.com/tpj/index.html>

DOĞAL METABOLİZMA HATALARI HAKKINDA BİLGİ

Blau N, Duran M, Blaskovics ME, Gibson KM. Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases (2nd ed.). Springer, 2002, 716 pp. ISBN 978-3-540-42542-7.
Blau N, Hoffmann GF, Leonard J, Clarke JTR. Physician's Guide to the Treatment and Follow-up of Metabolic Disease (1st ed.). Springer, 2006, 416 pp. ISBN 3-540-22954-X.
Scriver's Online Metabolic & Molecular Bases of Inherited Diseases, <http://www.ommbid.com/>

GEN BİLGİSİ

Disease descriptions, glossary, and lab directory, <http://www.ncbi.nlm.nih.gov/sites/GeneTests/>
National Library of Medicine, gene information, <http://www.ncbi.nlm.nih.gov/sites/entrez?db¼gene>
Online Mendelian Inheritance in Man (OMIM), comprehensive gene information, <http://www.omim.org/>

VERİTABANLARI

1000 Genomes Project, <http://www.1000genomes.org>
Catalogue of GWAS, <http://www.genome.gov/gwastudies/>

Database of Genomic Variants, The Centre for Applied Genomics, Toronto, <http://projects.tcag.ca/variation/>
 HapMap, <http://www.hapmap.org/>
 Micronutrient-related pathways, <http://micronutrients.wikipathways.org>
 NHLBI Exome Sequencing Project (ESP) Exome Variant Server (accessed June 2012), <http://evs.gs.washington.edu/EVS/>
 OpenSNP, <http://opensnp.org/> searchable by rs number, gives position on chromosome and in gene
 SNPedia for allele frequencies, <http://www.snpedia.com>

VERİ MADENCİLİĞİ VE GÖRÜNTÜLEME ARAÇLARI

dbSNP, <http://www.ncbi.nlm.nih.gov/projects/SNP/>
 Display linkage disequilibrium and recombination, <https://statgen.sph.umich.edu/locuszoom/genform.php?type¼ourdata>
 Ensemble, <http://www.ensembl.org>
 Entrez Gene, <http://www.ncbi.nlm.nih.gov/sites/entrez?db¼gene>
 GEN2PHEN Project, <http://www.gen2phen.org/>
 GenBank, <http://www.ncbi.nlm.nih.gov/Genbank/>
 Genetic Association Database, <http://geneticassociationdb.nih.gov/>
 HuGE Literature Finder, <http://www.hugenavigator.net/HuGENavigator/startPagePubLit.do>
 HuGE Navigator GWAS Integrator, <http://hugenavigator.net/HuGENavigator/gWAHitStartPage.do>
 Human Gene Coexpression Database, <http://www.geneticsofgeneexpression.org/network/>
 Integrative Genomics Viewer, tool for displaying associations, http://www.ncbi.nlm.nih.gov/projects/gapplusprev/sgap_plus.htm
 National Center for Biotechnology Information (NCBI), <http://www.ncbi.nlm.nih.gov/>
 Phenotype-Genotype Integrator, <http://www.ncbi.nlm.nih.gov/gap/PheGenI>
 PhenX Toolkit (consensus measures of Phenotypes and eXposures), <http://www.phenxtoolkit.org>
 PolyPhen, tool for the exploration of the possible impact of amino acid variation on protein function, <http://genetics.bwh.harvard.edu/pph/>
 PubMed, <http://www.ncbi.nlm.nih.gov/sites/entrez/>
 Variant Name Mapper, <http://www.hugenavigator.net/HuGENavigator/startPageMapper.do>

GENETİK YAZILIM PAKETLERİ

HAPSTAT: Statistical analysis of haplotype-disease associations, <http://www.bios.unc.edu/~dlin/hapstat/>
 ISHAPE and SHAPEIT: Accelerated and verified haplotype analysis programs [1], <http://www.griv.org/ishape/> and <http://www.shapeit.fr/>

PEDCHECK software: Examine variants for Mendelian inconsistencies [2], <http://watson.hgen.pitt.edu/register/>
PREST software: Pedigree RElationship Statistical Test [3], <http://fisher.outstat.toronto.edu/sun/Software/Prest>
S.A.G.E.: Statistical Analysis for Genetic Epidemiology, open source software for the genetic analysis of family, pedigree and individual data, <http://darwin.cwru.edu/sage/>
SOLAR software: Sequential Oligogenic Linkage Analysis Routines, for estimating residual heritability [4], <http://www.txbiomed.org/departments/genetics/genetics-detail?p¼37>

KAYNAKLAR

- [1] Delaneau O, Coulonges C, Boelle PY, Nelson G, Spadoni JL, Zagury JF. ISHAPE: new rapid and accurate software for haplotyping. *BMC Bioinformatics* 2007;8:205.
- [2] O'Connell JR, Weeks DE. PedCheck: a program for identification of genotype incompatibilities in linkage analysis. *Am J Hum Genet* 1998;63(1):259e66.
- [3] McPeck MS, Sun L. Statistical tests for detection of misspecified relationships by use of genome-screen data. *Am J Hum Genet* 2000;66(3):1076e94.
- [4] Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet* 1998;62(5):1198e211. Resources 367

BÖLÜM 1

Genotip Temelli Beslenme Kararları için Zaman Geldi mi?

“Tüm beslenme kalıtsaldır; genlerim bana bunu yaptırıyor.”

Martin Kohlmeier

TERİMLER

- Nutrigenetik: Genetik yatkınlığa bağlı olarak değişen beslenme durumu
- OMIM: İnsanlarda Çevrimiçi Mendel Kalıtım, bilinen tüm genlerin ve genetik hastalıkların bir kataloğu.

ÖZET

Beslenme birçok açıdan kişiseldir. Her birimizdeki farklı metabolik ve fonksiyonel değişen noktalar, bizim için en uygun besin çeşitlerini ve miktarlarını belirler. Bu kişisel beslenme değişkenleri, geçmiş ve şimdiki yaşamımızın koşulları kadar genetik planımıza da bağlıdır. Bu plana karşı çıkmak bazen olumsuz sağlık sonuçlarına neden olabilir. Dahası, uygun olmayan alımdan kaynaklanan herhangi bir zarar daha az belirgin, ancak zaman içinde yine de önemli olacaktır. Yeni olan, genetik plan sayesinde, her bir birey için detaylı beslenme düzeninden hangisinin en iyi olduğunu tahmin etme yeteneğimizdir.

1.1 YAŞAM FESTİVAL DEĞİLDİR

1.1.1 Hepimiz Benzeriz Ama Aynı Değiliz

Son derece karmaşık ve ince ayarlanmış organizmalarız ve bedenlerimiz büyük özveriyi hak ediyor. Amerikalılar için Beslenme Rehberi [1] birçok harika ipucu sunmaktadır. Örneğin, ‘rafine edilmiş tahılların yerine tam tahıllar konulmalıdır, böylece tüketilen tahılların en az yarısı tam tahıllardan oluşur’. Bu kesinlikle birçoğu için sağlıklı bir tavsiyedir, ama gerçekten hepimiz için geçerli mi? Başka bir vücut koruma kılavuzu (Diyet Referans Alımları) [2] bize folat alımını anlatıyor: ‘Gebe kalabilen tüm kadınların, çeşitli diyetlerden besin folatı alımının yanı sıra takviyelerden veya takviye edilmiş besinlerden 400 mg tüketmesi önerilir’. Ama sonra bedenlerimizin aynı olmadığını hatırlıyoruz. Uzun veya kısa boylu, ağır kemikli veya minyon olmak, tek tek listelemek için çok fazla farkımız var

ÖZET VE SONRAKİ BÖLÜME GEÇİŞ

Bu bölüm, insan genomunun mimarisinin yanı sıra transkripsiyon ve çeviri mekanizmaları da dahil olmak üzere kalıtımın biyolojik temelini yeniden gözden geçirmiştir. Aynı zamanda, genellikle maternal ve paternal kromozom kopyalarında bulunan alelleri sayarak takip edilebilen ortak genetik bulaşma modlarını da inceledik. Bazen, her bir ebeveyninden farklı sayıda kopyanın mirası, bir ebeveyn gen kopyasının yokluğu, epigenetik mekanizmalar yoluyla bulaşma veya çok nadir durumlarda anne mtDNA'sı yoluyla kalıtım gibi durumlara açıklanabilecek daha karmaşık bir kalıtım modeli buluruz.

Şimdi beslenmeyi etkileyen genetik varyasyonun nereden geldiğini incelemeye devam edeceğiz. Bir sonraki bölüm, hangi besinlerin bizim için en iyi olduğunu etkileyen bazı genetik varyantların kökenlerini araştıracaktır. Paleolitik diyetlerin doğası, çoğu Çinlinin alkol almamaya ikna ettiği ve 800 yıl önce çoğu Paskalya Adalı'nın haptogloblin varyantı Hp1'e nasıl geldiğine dair hayati meselelere değineceğiz.

KAYNAKLAR

- [1] Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. *Horm Behav* 2011 Mar;59(3):290e5.
- [2] Yazbek SN, Spiezio SH, Nadeau JH, Buchner DA. Ancestral paternal genotype controls body weight and food intake for multiple generations. *Hum Mol Genet* 2010 Nov 1;19(21): 4134e44.
- [3] Globisch D, Munzel M, Muller M, Michalakakis S, Wagner M, Koch S, et al. Tissue distribution of 5-hydroxymethylcytosine and search for active demethylation intermediates. *PLoS One* 2010;5(12): e15367.
- [4] Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, et al. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. *Science* 2011 Jul 21;33(6047): 1300e3.
- [5] Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. *Nature* 2001;409(6822):860e921.
- [6] Taylor RW, Taylor GA, Durham SE, Turnbull DM. The determination of complete human mitochondrial DNA sequences in single cells: implications for the study of somatic mitochondrial DNA point mutations. *Nucleic Acids Res* 2001 Aug 1;29(15):E74e4.
- [7] Eynon N, Moran M, Birk R, Lucia A. The champions' mitochondria: is it genetically determined? A review on mitochondrial DNA and elite athletic performance. *Physiol Genomics* 2011 Jul 14;43(13):789e98.
- [8] Reiner JE, Kishore RB, Levin BC, Albanetti T, Boire N, Knipe A, et al. Detection of heteroplasmic mitochondrial DNA in single mitochondria. *PLoS One* 2010;5(12):e14359.
- [9] Ivanov PL, Wadhams MJ, Roby RK, Holland MM, Weedn VW, Parsons TJ. Mitochondrial DNA sequence heteroplasmy in the Grand Duke of Russia Georgij Romanov establishes the authenticity of the remains of Tsar Nicholas II. *Nat Genet* 1996 Apr;12(4):417e20.
- [10] Irwin JA, Saunier JL, Niederstatter H, Strouss KM, Sturk KA, Diegoli TM, et al. Investigation of heteroplasmy in the human mitochondrial DNA control region: a synthesis of observations from more than 5000 global population samples. *J Mol Evol* 2009 May;68(5): 516e27.
- [11] Cooper-Brown L, Copeland S, Dailey S, Downey D, Petersen MC, Stimson C, et al. Feeding and swallowing dysfunction in genetic syndromes. *Dev Disabil Res Rev* 2008;14(2):147e57.
- [12] Gonzalez-Aguero A, Ara I, Moreno LA, Vicente-Rodriguez G, Casajus JA. Fat and lean masses in youths with Down syndrome: Gender differences. *Res Dev Disabil* 2011 Sep-Oct;32(5): 1685e93.
- [13] Marreiro Ddo N, de Sousa AF, Nogueira Ndo N, Oliveira FE. Effect of zinc supplementation on thyroid hormone metabolism of adolescents with Down syndrome. *Biol Trace Elem Res*

2009;129(1e3):20e7.

- [14] Book L, Hart A, Black J, Feolo M, Zone JJ, Neuhausen SL. Prevalence and clinical characteristics of celiac disease in Down syndrome in a US study. *Am J Med Genet* 2001 Jan 1;98(1): 70e4.
- [15] Shamaly H, Hartman C, Pollack S, Hujerat M, Katz R, Gideoni O, et al. Tissue transglutaminase antibodies are a useful serological marker for the diagnosis of celiac disease in patients with Down syndrome. *J Pediatr Gastroenterol Nutr* 2007 May;44(5):583e6.
- [16] Cerqueira RM, Rocha CM, Fernandes CD, Correia MR. Celiac disease in Portuguese children and adults with Down syndrome. *Eur J Gastroenterol Hepatol* 2010 Jul;22(7):868e71.
- [17] Wouters J, Weijerman ME, van Furth AM, Schreurs MW, Crusius JB, von Blomberg BM, et al. Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down syndrome. *J Pediatr* 2009 Feb;154(2):239e42.
- [18] Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ. Homocysteine metabolism in children with Down syndrome: in vitro modulation. *Am J Hum Genet* 2001 Jul;69(1): 88e95.
- [19] Locke AE, Dooley KJ, Tinker SW, Cheong SY, Feingold E, Allen EG, et al. Variation in folate pathway genes contributes to risk of congenital heart defects among individuals with Down syndrome. *Genet Epidemiol* 2010 Sep;34(6):613e23.
- [20] Gumus H, Ghesquiere S, Per H, Kondolot M, Ichida K, Poyrazoglu G, et al. Maternal uniparental isodisomy is responsible for serious molybdenum cofactor deficiency. *Dev Med Child Neurol* 2010 Sep;52(9):868e72.
- [21] Sun F, Oliver-Bonet M, Liehr T, Starke H, Ko E, Rademaker A, et al. Human male recombination maps for individual chromosomes. *Am J Hum Genet* 2004 Mar;74(3):521e31.
- [22] Kong A, Thorleifsson G, Gudbjartsson DF, Masson G, Sigurdsson A, Jonasdottir A, et al. Fine-scale recombination rate differences between sexes, populations and individuals. *Nature* 2010 Oct 28;467(7319):1099e103.
- [23] Slatkin MA. Bayesian method for jointly estimating allele age and selection intensity. *Genet Res (Camb)* 2008 Feb;90(1):129e37.
- [24] Mills RE, Walter K, Stewart C, Handsaker RE, Chen K, Alkan C, et al. Mapping copy number variation by population-scale genome sequencing. *Nature* 2011 Feb 3;470(7332):59e65.
- [25] Deuve JL, Avner P. The coupling of X-chromosome inactivation to pluripotency. *Annu Rev Cell Dev Biol* 2011 Nov 10;27:611e29.
- [26] Hanna JH, Saha K, Jaenisch R. Pluripotency and cellular reprogramming: facts, hypotheses, unresolved issues. *Cell* 2010 Nov 12;143(4):508e25.
- [27] Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr* 2010 Aug 21;30:315e39.
- [28] Dhawan S, Georgia S, Tschen SI, Fan G, Bhushan A. Pancreatic beta cell identity is maintained by DNA methylation-mediated repression of *Arx*. *Dev Cell* 2011 Apr 19;20(4): 419e29.
- [29] Fenech MF. Dietary reference values of individual micronutrients and nutrionics for genome damage prevention: current status and a road map to the future. *Am J Clin Nutr* 2010 May;91(5):1438Se54S.
- [30] Stidley CA, Picchi MA, Leng S, Willink R, Crowell RE, Flores KG, et al. Multivitamins, folate, and green vegetables protect against gene promoter methylation in the aerodigestive tract of smokers. *Cancer Res* 2010 Jan 15;70(2):568e74.
- [31] Kim HS, Smithies O, Maeda N. A physical map of the human salivary proline-rich protein gene cluster covers over 700 kbp of DNA. *Genomics* 1990 Feb;6(2):260e7.
- [32] Lyon MF. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature* 1961 Apr 22;190:372e3.
- [33] Tattermusch A, Brockdorff N. A scaffold for X chromosome inactivation. *Hum Genet* 2011 Aug;130(2):247e53.
- [34] Lopez V, Kelleher SL. Zinc transporter-2 (ZnT2) variants are localized to distinct subcellular compartments and functionally transport zinc. *Biochem J* 2009;422(1):43e52.

- [35] Roll-Hansen N. The genotype theory of Wilhelm Johannsen and its relation to plant breeding and the study of evolution. *Centaurus* 1979;22:201e35.
- [36] Reed DR, Zhu G, Breslin PA, Duke FF, Henders AK, Campbell MJ, et al. The perception of quinine taste intensity is associated with common genetic variants in a bitter receptor cluster on chromosome 12. *Hum Mol Genet* 2010 Nov 1;19(21):4278e85.
- [37] Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bartoshuk LM, Duffy VB. Alelic variation in TAS2R bitter receptor genes associates with variation in sensations from and ingestive behaviors toward common bitter beverages in adults. *Chem Senses* 2011 Mar;36(3):311e19.
- [38] Palmieri VO, De Rasmio D, Signorile A, Sardanelli AM, Grattagliano I, Minerva F, et al. T16189C mitochondrial DNA variant is associated with metabolic syndrome in Caucasian subjects. *Nutrition* 2011 Jul-Aug;27(7e8):773e7.
- [39] Liou CW, Lin TK, Huei Weng H, Lee CF, Chen TL, Wei YH, et al. A common mitochondrial DNA variant and increased body mass index as associated factors for development of type 2 diabetes: Additive effects of genetic and environmental factors. *J Clin Endocrinol Metab* 2007 Jan;92(1):235e9.
- [40] Mueller EE, Eder W, Ebner S, Schwaiger E, Santic D, Kreindl T, et al. The mitochondrial T16189C polymorphism is associated with coronary artery disease in Middle European populations. *PLoS One* 2011;6(1):e16455.
- [41] Wilson FH, Hariri A, Farhi A, Zhao H, Petersen KF, Toka HR, et al. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. *Science* 2004 Nov 12;306(5699): 1190e4.
- [42] Donkena KV, Yuan H, Young CY. Vitamin Bs, one carbon metabolism and prostate cancer. *Mini Rev Med Chem* 2010 Dec;10(14):1385e92.
- [43] Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab* 2010 Apr;21(4):214e22.
- [44] Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med* 2012 Jan;14(1):10e26.
- [45] Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. *Endocrinology* 2011 Jun;152(6):2228e36.
- [46] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 2008 Nov 4;105(44):17046e9.
- [47] Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S. Methyl donor supplementation prevents transgenerational amplification of obesity. *Int J Obes (Lond)* 2008 Sep;32(9): 1373e9.
- [48] Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet* 2009 Nov 1;18(21):4046e53.
- [49] Kaati G, Bygren LO, Pembrey M, Sjöström M. Transgenerational response to nutrition, early life circumstances and longevity. *Eur J Hum Genet* 2007 Jul;15(7):784e90.
- [50] Bygren LO, Kaati G, Edvinsson S. Longevity determined by paternal ancestors' nutrition during their slow growth period. *Acta Biotheor* 2001 Mar;49(1):53e9.
- [51] Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 2007 Apr;8(4):253e62.
- [52] Moonesinghe R, Yesupriya A, Chang MH, Dowling NF, Khoury MJ, Scott AJ. A Hardy-Weinberg equilibrium test for analyzing population genetic surveys with complex sample designs. *Am J Epidemiol* 2010 Apr 15;171(8):932e41.
- [53] Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *Proc Natl Acad Sci U S A* 2005 Nov 1;102(44):16025e30.
- [54] 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* 2010 Oct 28;467(7319):1061e73.

- [55] Lachance J. Disease-associated alleles in genome-wide association studies are enriched for derived low frequency alleles relative to HapMap and neutral expectations. *BMC Med Genomics* 2010;3:57.
- [56] Carroll N, Pangilinan F, Molloy AM, Troendle J, Mills JL, Kirke PN, et al. Analysis of the MTHFD1 promoter and risk of neural tube defects. *Hum Genet* 2009 Apr;125(3):247e56.
- [57] Slatkin M. Linkage disequilibrium understanding the evolutionary past and mapping the medical future. *Nat Rev Genet* 2008 Jun;9(6):477e85.
- [58] Kohlmeier M, Saupe J, Schaefer K, Asmus G. Bone fracture history and prospective bone fracture risk of hemodialysis patients are related to apolipoprotein E genotype. *Calcif Tissue Int* 1998 Mar;62(3):278e81.
- [59] Lambert JC, Brousseau T, Defosse V, Evans A, Arveiler D, Ruidavets JB, et al. Independent association of an APOE gene promoter polymorphism with increased risk of myocardial infarction and decreased APOE plasma concentrations in the ECTIM study. *Hum Mol Genet* 2000 Jan 1;9(1):57e61.
- [60] Hanlon CS, Rubinsztein DC. Arginine residues at codons 112 and 158 in the apolipoprotein E gene correspond to the ancestral state in humans. *Atherosclerosis* 1995 Jan 6;112(1): 85e90.
- [61] Kohlmeier M, Salomon A, Saupe J, Shearer MJ. Transport of vitamin K to bone in humans. *J Nutr* 1996 Apr;126(Suppl. 4):1192Se6S.
- [62] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993 Aug 13;261(5123):921e3.
- [63] Ward H, Mitrou PN, Bowman R, Luben R, Wareham NJ, Khaw KT, et al. APOE genotype, lipids, and coronary heart disease risk: a prospective population study. *Arch Intern Med* 2009 Aug 10;169(15):1424e9.
- [64] Lescai F, Chiamenti AM, Codemo A, Pirazzini C, D'Agostino G, Ruaro C, et al. An APOE haplotype associated with decreased epsilon4 expression increases the risk of late onset Alzheimer's disease. *J Alzheimers Dis* 2011;24(2):235e45.
- [65] Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. *Mol Biol Evol* 1995 Sep;12(5):921e7.
- [66] Nielsen DM, Ehm MG, Zaykin DV, Weir BS. Effect of two- and three-locus linkage disequilibrium on the power to detect marker/phenotype associations. *Genetics* 2004 Oct;168(2): 1029e40.
- [67] Martin YN, Salavaggione OE, Eckloff BW, Wieben ED, Schaid DJ, Weinshilboum RM. Human methylenetetrahydrofolate reductase pharmacogenomics: gene resequencing and functional genomics. *Pharmacogenet Genomics* 2006 Apr;16(4):265e77.
- [68] Guenther BD, Sheppard CA, Tran P, Rozen R, Matthews RG, Ludwig ML. The structure and properties of methylenetetrahydrofolate reductase from *Escherichia coli* suggest how folate ameliorates human hyperhomocysteinemia. *Nat Struct Biol* 1999 Apr;6(4):359e65.
- [69] Richter RJ, Jarvik GP, Furlong CE. Paraoxonase 1 (PON1) status and substrate hydrolysis. *Toxicol Appl Pharmacol* 2009 Feb 15;235(1):1e9.
- [70] Chamary JV, Hurst LD. Evidence for selection on synonymous mutations affecting stability of mRNA secondary structure in mammals. *Genome Biol* 2005;6(9):R75.
- [71] Resch AM, Carmel L, Marino-Ramirez L, Ogurtsov AY, Shabalina SA, Rogozin IB, et al. Widespread positive selection in synonymous sites of mammalian genes. *Mol Biol Evol* 2007 Aug;24(8):1821e31.
- [72] Wang D, Sadee W. Searching for polymorphisms that affect gene expression and mRNA processing: example ABCB1 (MDR1). *AAPS J* 2006;8(3):E515e20.
- [73] Defesche JC, Schuurman EJ, Klaijns LN, Khoo KL, Wiegman A, Stalenhoef AF. Silent exonic mutations in the low-density lipoprotein receptor gene that cause familial hypercholesterolemia by affecting mRNA splicing. *Clin Genet* 2008 Jun;73(6):573e8.
- [74] Livingstone M, Atas E, Meller A, Sonenberg N. Mechanisms governing the control of mRNA translation. *Phys Biol* 2010;7(2):021001.

- [75] Mazumder B, Seshadri V, Fox PL. Translational control by the 30-UTR: the ends specify the means. *Trends Biochem Sci* 2003 Feb;28(2):91e8.
- [76] Mishra PJ, Humeniuk R, Longo-Sorbello GS, Banerjee D, Bertino JR. A miR-24 microRNA binding-site polymorphism in dihydrofolate reductase gene leads to methotrexate resistance. *Proc Natl Acad Sci U S A* 2007 Aug 14;104(33):13513e18.
- [77] Vikman S, Brena RM, Armstrong P, Hartiala J, Stephensen CB, Allayee H. Functional analysis of 5-lipoxygenase promoter repeat variants. *Hum Mol Genet* 2009 Dec 1;18(23):4521e9.
- [78] Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med* 2004 Jan 1;350(1):29e37.
- [79] Parle-McDermott A, Pangilinan F, O'Brien KK, Mills JL, Magee AM, Troendle J, et al. A common variant in MTHFD1L is associated with neural tube defects and mRNA splicing efficiency. *Hum Mutat* 2009 Dec;30(12):1650e6.
- [80] Sudmant PH, Kitzman JO, Antonacci F, Alkan C, Malig M, Tsalenko A, et al. Diversity of human copy number variation and multicopy genes. *Science* 2010 Oct 29;330(6004):641e6.
- [81] Stamoulis C, Betensky RA. A novel signal processing approach for the detection of copy-number variations in the human genome. *Bioinformatics* 2011 Jul 12.
- [82] Varma V, Wise C, Kaput J. Carbohydrate metabolic pathway genes associated with quantitative trait loci (QTL) for obesity and type 2 diabetes: identification by data mining. *Biotechnol J* 2010 Sep;5(9):942e9.
- [83] Sindi SS, Raphael BJ. Identification and frequency estimation of inversion polymorphisms from haplotype data. *J Comput Biol* 2010 Mar;17(3):517e31.
- [84] Naylor JA, Nicholson P, Goodeve A, Hassock S, Peake I, Giannelli F. A novel DNA inversion causing severe hemophilia A. *Blood* 1996 Apr 15;87(8):3255e61.
- [85] Yamaguchi-Kabata Y, Shimada MK, Hayakawa Y, Minoshima S, Chakraborty R, Gojobori T, et al. Distribution and effects of nonsense polymorphisms in human genes. *PLoS One* 2008;3(10):e3393.
- [86] Gordon N. Ornithine transcarbamylase deficiency: a urea cycle defect. *Eur J Paediatr Neurol* 2003;7(3):115e21.
- [87] Blau N, Scherer-Oppliger T, Baumer A, Riegel M, Matasovic A, Schinzel A, et al. Isolated central form of tetrahydrobiopterin deficiency associated with hemizygoty on chromosome 11q and a mutant allele of PTPS. *Hum Mutat* 2000;16(1):54e60.
- [88] Roudnitzky N, Bufe B, Thalmann S, Kuhn C, Gunn HC, Xing C, et al. Genomic, genetic and functional dissection of bitter taste responses to artificial sweeteners. *Hum Mol Genet* 2011 Sep 1;20(17):3437e49.
- [89] Hosking FJ, Papaemmanuil E, Sheridan E, Kinsey SE, Lightfoot T, Roman E, et al. Genome-wide homozygosity signatures and childhood acute lymphoblastic leukemia risk. *Blood* 2010 Jun 3;115(22):4472e7.
- [90] Martin DI, Cropley JE, Suter CM. Epigenetics in disease: Leader or follower? *Epigenetics* 2011 Jul 1;6(7):843e8.
- [91] Hitchins M, Owens S, Kwok CT, Godsmark G, Algar U, Ramesar R. Identification of new cases of early-onset colorectal cancer with an MLH1 epimutation in an ethnically diverse South African cohort(dagger). *Clin Genet* 2011 Nov;80(5):428e34.
- [92] Shibui T, Higo Y, Tsutsui TW, Uchida M, Oshimura M, Barrett JC, et al. Changes in expression of imprinted genes following treatment of human cancer cell lines with non-mutagenic or mutagenic carcinogens. *Int J Oncol* 2008 Aug;33(2):351e60.

BÖLÜM 2

Genetik Geçiş Nasıl Çalışır?

TERİMLER

- Aleller: Bir lokusta alternatif DNA dizileri.
- Otozomal: Sayılı kromozomların birinin kalıtsallıkla ilişkisi.
- Cis: Aynı DNA zincirinden geliyor veya aynı DNA zincirinde bulunuyor.
- Diplotip: Bireyin iki haplotipine gönderme.
- Baskın: Özelliğin her zaman diğerini geçersiz kıldığı kalıtım modu heterozigot durumda (resesif) özellik.
- Epigenetik: Geni etkileyen kimyasal DNA değişikliklerine ilişkin ifadesi.
- Ekzon: Bir gen içindeki proteine çevrilen bir DNA segmenti.
- Genotip: Bir gen lokusunda kalıtsal varyantların kombinasyonu.
- Haplotip: Aynı iplikteki alellerin kombinasyonu.
- Hemizigot: İkinci bir kopya olmadığında bir aleli taşımak.
- Kalıtım derecesi: Bir özelliğin kalıtım yoluyla alındığı tahmini yüzde.
- Heteroplazmi: Bir baba atadan miras alınan mitokondri varlığı.
- Heterozigot: Bir kromozom çiftinde farklı aleller taşımak.
- Homozigot: Bir kromozom çifti üzerinde aynı varyant formları (aleller) taşımak.
- İntron: Eksonlar arasında bulunan çevrilmemiş DNA segmenti.
- Bağlantı dengesizliği: İki alelin istatistiksel ilişkisi.
- Odağı (pl. loci): Bir kromozom üzerindeki spesifik lokal sekans.
- LoD: İki loci arasındaki mesafeyi tahmin etmek için sıklıkla kullanılan oran logaritması.
- Memetik kalıtım: Yöntem ve davranışların bir kişiden bulaşması başka bir.
- Fenotip: Dış veya biyolojik görünüm.
- Polimorfizm: Bir popülasyonun en az %1'inde meydana gelen varyant.
- Resesif: Özelliğin her zaman diğeri tarafından geçersiz kıldığı kalıtım modu heterozigot durumda (baskın) özellik.
- Trans: Farklı bir DNA zincirinden geliyor veya farklı bir DNA şeridinde yerleştiriliyor.
- Transkripsiyon: Nükleer DNA segmentlerinden haberci RNA sentezi.
- Çeviri: Haberci RNA şablonlarından protein sentezi.

ÖZET VE SONRAKİ BÖLÜME GEÇİŞ

Bu bölüm, insan genomunun mimarisinin yanı sıra transkripsiyon ve çeviri mekanizmaları da dahil olmak üzere kalıtımın biyolojik temelini yeniden gözden geçirmiştir. Aynı zamanda, genellikle maternal ve paternal kromozom kopyalarında bulunan alelleri sayarak takip edilebilen ortak genetik bulaşma modlarını da inceledik. Bazen, her bir ebeveyninden farklı sayıda kopyanın mirası, bir ebeveyn gen kopyasının yokluğu, epigenetik mekanizmalar yoluyla bulaşma veya çok nadir durumlarda anne mtDNA'sı yoluyla kalıtım gibi durumlarla açıklanabilecek daha karmaşık bir kalıtım modeli buluruz.

Şimdi beslenmeyi etkileyen genetik varyasyonun nereden geldiğini incelemeye devam edeceğiz. Bir sonraki bölüm, hangi besinlerin bizim için en iyi olduğunu etkileyen bazı genetik varyantların kökenlerini araştıracaktır. Paleolitik diyetlerin doğası, çoğu Çinlinin alkol almamaya ikna ettiği ve 800 yıl önce çoğu Paskalya Adalı'nın haptogloblin varyantı Hp1'e nasıl geldiğine dair hayati meselelere değineceğiz.

KAYNAKLAR

- [1] Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. *Horm Behav* 2011 Mar;59(3):290e5.
- [2] Yazbek SN, Spiezio SH, Nadeau JH, Buchner DA. Ancestral paternal genotype controls body weight and food intake for multiple generations. *Hum Mol Genet* 2010 Nov 1;19(21): 4134e44.
- [3] Globisch D, Munzel M, Muller M, Michalakakis S, Wagner M, Koch S, et al. Tissue distribution of 5-hydroxymethylcytosine and search for active demethylation intermediates. *PLoS One* 2010;5(12): e15367.
- [4] Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, et al. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. *Science* 2011 Jul 21;33(6047): 1300e3.
- [5] Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. *Nature* 2001;409(6822):860e921.
- [6] Taylor RW, Taylor GA, Durham SE, Turnbull DM. The determination of complete human mitochondrial DNA sequences in single cells: implications for the study of somatic mitochondrial DNA point mutations. *Nucleic Acids Res* 2001 Aug 1;29(15):E74e4.
- [7] Eynon N, Moran M, Birk R, Lucia A. The champions' mitochondria: is it genetically determined? A review on mitochondrial DNA and elite athletic performance. *Physiol Genomics* 2011 Jul 14;43(13):789e98.
- [8] Reiner JE, Kishore RB, Levin BC, Albanetti T, Boire N, Knipe A, et al. Detection of heteroplasmic mitochondrial DNA in single mitochondria. *PLoS One* 2010;5(12):e14359.
- [9] Ivanov PL, Wadhams MJ, Roby RK, Holland MM, Weedn VW, Parsons TJ. Mitochondrial DNA sequence heteroplasmy in the Grand Duke of Russia Georgij Romanov establishes the authenticity of the remains of Tsar Nicholas II. *Nat Genet* 1996 Apr;12(4):417e20.
- [10] Irwin JA, Saunier JL, Niederstatter H, Strouss KM, Sturk KA, Diegoli TM, et al. Investigation of heteroplasmy in the human mitochondrial DNA control region: a synthesis of observations from more than 5000 global population samples. *J Mol Evol* 2009 May;68(5): 516e27.
- [11] Cooper-Brown L, Copeland S, Dailey S, Downey D, Petersen MC, Stimson C, et al. Feeding and swallowing dysfunction in genetic syndromes. *Dev Disabil Res Rev* 2008;14(2):147e57.
- [12] Gonzalez-Aguero A, Ara I, Moreno LA, Vicente-Rodriguez G, Casajus JA. Fat and lean masses in youths with Down syndrome: Gender differences. *Res Dev Disabil* 2011 Sep-Oct;32(5): 1685e93.
- [13] Marreiro Ddo N, de Sousa AF, Nogueira Ndo N, Oliveira FE. Effect of zinc supplementation on thyroid hormone metabolism of adolescents with Down syndrome. *Biol Trace Elem Res*

2009;129(1e3):20e7.

- [14] Book L, Hart A, Black J, Feolo M, Zone JJ, Neuhausen SL. Prevalence and clinical characteristics of celiac disease in Down syndrome in a US study. *Am J Med Genet* 2001 Jan 1;98(1): 70e4.
- [15] Shamaly H, Hartman C, Pollack S, Hujerat M, Katz R, Gideoni O, et al. Tissue transglutaminase antibodies are a useful serological marker for the diagnosis of celiac disease in patients with Down syndrome. *J Pediatr Gastroenterol Nutr* 2007 May;44(5):583e6.
- [16] Cerqueira RM, Rocha CM, Fernandes CD, Correia MR. Celiac disease in Portuguese children and adults with Down syndrome. *Eur J Gastroenterol Hepatol* 2010 Jul;22(7):868e71.
- [17] Wouters J, Weijerman ME, van Furth AM, Schreurs MW, Crusius JB, von Blomberg BM, et al. Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down syndrome. *J Pediatr* 2009 Feb;154(2):239e42.
- [18] Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ. Homocysteine metabolism in children with Down syndrome: in vitro modulation. *Am J Hum Genet* 2001 Jul;69(1): 88e95.
- [19] Locke AE, Dooley KJ, Tinker SW, Cheong SY, Feingold E, Allen EG, et al. Variation in folate pathway genes contributes to risk of congenital heart defects among individuals with Down syndrome. *Genet Epidemiol* 2010 Sep;34(6):613e23.
- [20] Gumus H, Ghesquiere S, Per H, Kondolot M, Ichida K, Poyrazoglu G, et al. Maternal uniparental isodisomy is responsible for serious molybdenum cofactor deficiency. *Dev Med Child Neurol* 2010 Sep;52(9):868e72.
- [21] Sun F, Oliver-Bonet M, Liehr T, Starke H, Ko E, Rademaker A, et al. Human male recombination maps for individual chromosomes. *Am J Hum Genet* 2004 Mar;74(3):521e31.
- [22] Kong A, Thorleifsson G, Gudbjartsson DF, Masson G, Sigurdsson A, Jonasdottir A, et al. Fine-scale recombination rate differences between sexes, populations and individuals. *Nature* 2010 Oct 28;467(7319):1099e103.
- [23] Slatkin MA. Bayesian method for jointly estimating allele age and selection intensity. *Genet Res (Camb)* 2008 Feb;90(1):129e37.
- [24] Mills RE, Walter K, Stewart C, Handsaker RE, Chen K, Alkan C, et al. Mapping copy number variation by population-scale genome sequencing. *Nature* 2011 Feb 3;470(7332):59e65.
- [25] Deuve JL, Avner P. The coupling of X-chromosome inactivation to pluripotency. *Annu Rev Cell Dev Biol* 2011 Nov 10;27:611e29.
- [26] Hanna JH, Saha K, Jaenisch R. Pluripotency and cellular reprogramming: facts, hypotheses, unresolved issues. *Cell* 2010 Nov 12;143(4):508e25.
- [27] Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr* 2010 Aug 21;30:315e39.
- [28] Dhawan S, Georgia S, Tschen SI, Fan G, Bhushan A. Pancreatic beta cell identity is maintained by DNA methylation-mediated repression of *Arx*. *Dev Cell* 2011 Apr 19;20(4): 419e29.
- [29] Fenech MF. Dietary reference values of individual micronutrients and nutraceuticals for genome damage prevention: current status and a road map to the future. *Am J Clin Nutr* 2010 May;91(5):1438Se54S.
- [30] Stidley CA, Picchi MA, Leng S, Willink R, Crowell RE, Flores KG, et al. Multivitamins, folate, and green vegetables protect against gene promoter methylation in the aerodigestive tract of smokers. *Cancer Res* 2010 Jan 15;70(2):568e74.
- [31] Kim HS, Smithies O, Maeda N. A physical map of the human salivary proline-rich protein gene cluster covers over 700 kbp of DNA. *Genomics* 1990 Feb;6(2):260e7.
- [32] Lyon MF. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature* 1961 Apr 22;190:372e3.
- [33] Tattermusch A, Brockdorff N. A scaffold for X chromosome inactivation. *Hum Genet* 2011 Aug;130(2):247e53.
- [34] Lopez V, Kelleher SL. Zinc transporter-2 (ZnT2) variants are localized to distinct subcellular compartments and functionally transport zinc. *Biochem J* 2009;422(1):43e52.

- [35] Roll-Hansen N. The genotype theory of Wilhelm Johannsen and its relation to plant breeding and the study of evolution. *Centaurus* 1979;22:201e35.
- [36] Reed DR, Zhu G, Breslin PA, Duke FF, Henders AK, Campbell MJ, et al. The perception of quinine taste intensity is associated with common genetic variants in a bitter receptor cluster on chromosome 12. *Hum Mol Genet* 2010 Nov 1;19(21):4278e85.
- [37] Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bartoshuk LM, Duffy VB. Alelic variation in TAS2R bitter receptor genes associates with variation in sensations from and ingestive behaviors toward common bitter beverages in adults. *Chem Senses* 2011 Mar;36(3):311e19.
- [38] Palmieri VO, De Rasmio D, Signorile A, Sardanelli AM, Grattagliano I, Minerva F, et al. T16189C mitochondrial DNA variant is associated with metabolic syndrome in Caucasian subjects. *Nutrition* 2011 Jul-Aug;27(7e8):773e7.
- [39] Liou CW, Lin TK, Huei Weng H, Lee CF, Chen TL, Wei YH, et al. A common mitochondrial DNA variant and increased body mass index as associated factors for development of type 2 diabetes: Additive effects of genetic and environmental factors. *J Clin Endocrinol Metab* 2007 Jan;92(1):235e9.
- [40] Mueller EE, Eder W, Ebner S, Schwaiger E, Santic D, Kreindl T, et al. The mitochondrial T16189C polymorphism is associated with coronary artery disease in Middle European populations. *PLoS One* 2011;6(1):e16455.
- [41] Wilson FH, Hariri A, Farhi A, Zhao H, Petersen KF, Toka HR, et al. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. *Science* 2004 Nov 12;306(5699): 1190e4.
- [42] Donkena KV, Yuan H, Young CY. Vitamin Bs, one carbon metabolism and prostate cancer. *Mini Rev Med Chem* 2010 Dec;10(14):1385e92.
- [43] Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab* 2010 Apr;21(4):214e22.
- [44] Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med* 2012 Jan;14(1):10e26.
- [45] Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. *Endocrinology* 2011 Jun;152(6):2228e36.
- [46] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 2008 Nov 4;105(44):17046e9.
- [47] Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S. Methyl donor supplementation prevents transgenerational amplification of obesity. *Int J Obes (Lond)* 2008 Sep;32(9): 1373e9.
- [48] Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet* 2009 Nov 1;18(21):4046e53.
- [49] Kaati G, Bygren LO, Pembrey M, Sjöström M. Transgenerational response to nutrition, early life circumstances and longevity. *Eur J Hum Genet* 2007 Jul;15(7):784e90.
- [50] Bygren LO, Kaati G, Edvinsson S. Longevity determined by paternal ancestors' nutrition during their slow growth period. *Acta Biotheor* 2001 Mar;49(1):53e9.
- [51] Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 2007 Apr;8(4):253e62.
- [52] Moonesinghe R, Yesupriya A, Chang MH, Dowling NF, Khoury MJ, Scott AJ. A Hardy-Weinberg equilibrium test for analyzing population genetic surveys with complex sample designs. *Am J Epidemiol* 2010 Apr 15;171(8):932e41.
- [53] Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *Proc Natl Acad Sci U S A* 2005 Nov 1;102(44):16025e30.
- [54] 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* 2010 Oct 28;467(7319):1061e73.

- [55] Lachance J. Disease-associated alleles in genome-wide association studies are enriched for derived low frequency alleles relative to HapMap and neutral expectations. *BMC Med Genomics* 2010;3:57.
- [56] Carroll N, Pangilinan F, Molloy AM, Troendle J, Mills JL, Kirke PN, et al. Analysis of the MTHFD1 promoter and risk of neural tube defects. *Hum Genet* 2009 Apr;125(3):247e56.
- [57] Slatkin M. Linkage disequilibrium understanding the evolutionary past and mapping the medical future. *Nat Rev Genet* 2008 Jun;9(6):477e85.
- [58] Kohlmeier M, Saupé J, Schaefer K, Asmus G. Bone fracture history and prospective bone fracture risk of hemodialysis patients are related to apolipoprotein E genotype. *Calcif Tissue Int* 1998 Mar;62(3):278e81.
- [59] Lambert JC, Brousseau T, Defosse V, Evans A, Arveiler D, Ruidavets JB, et al. Independent association of an APOE gene promoter polymorphism with increased risk of myocardial infarction and decreased APOE plasma concentrations in the ECTIM study. *Hum Mol Genet* 2000 Jan 1;9(1):57e61.
- [60] Hanlon CS, Rubinsztein DC. Arginine residues at codons 112 and 158 in the apolipoprotein E gene correspond to the ancestral state in humans. *Atherosclerosis* 1995 Jan 6;112(1): 85e90.
- [61] Kohlmeier M, Salomon A, Saupé J, Shearer MJ. Transport of vitamin K to bone in humans. *J Nutr* 1996 Apr;126(Suppl. 4):1192Se6S.
- [62] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993 Aug 13;261(5123):921e3.
- [63] Ward H, Mitrou PN, Bowman R, Luben R, Wareham NJ, Khaw KT, et al. APOE genotype, lipids, and coronary heart disease risk: a prospective population study. *Arch Intern Med* 2009 Aug 10;169(15):1424e9.
- [64] Lescai F, Chiamenti AM, Codemo A, Pirazzini C, D'Agostino G, Ruaro C, et al. An APOE haplotype associated with decreased epsilon4 expression increases the risk of late onset Alzheimer's disease. *J Alzheimers Dis* 2011;24(2):235e45.
- [65] Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. *Mol Biol Evol* 1995 Sep;12(5):921e7.
- [66] Nielsen DM, Ehm MG, Zaykin DV, Weir BS. Effect of two- and three-locus linkage disequilibrium on the power to detect marker/phenotype associations. *Genetics* 2004 Oct;168(2): 1029e40.
- [67] Martin YN, Salavaggione OE, Eckloff BW, Wieben ED, Schaid DJ, Weinshilboum RM. Human methylenetetrahydrofolate reductase pharmacogenomics: gene resequencing and functional genomics. *Pharmacogenet Genomics* 2006 Apr;16(4):265e77.
- [68] Guenther BD, Sheppard CA, Tran P, Rozen R, Matthews RG, Ludwig ML. The structure and properties of methylenetetrahydrofolate reductase from *Escherichia coli* suggest how folate ameliorates human hyperhomocysteinemia. *Nat Struct Biol* 1999 Apr;6(4):359e65.
- [69] Richter RJ, Jarvik GP, Furlong CE. Paraoxonase 1 (PON1) status and substrate hydrolysis. *Toxicol Appl Pharmacol* 2009 Feb 15;235(1):1e9.
- [70] Chamary JV, Hurst LD. Evidence for selection on synonymous mutations affecting stability of mRNA secondary structure in mammals. *Genome Biol* 2005;6(9):R75.
- [71] Resch AM, Carmel L, Marino-Ramirez L, Ogurtsov AY, Shabalina SA, Rogozin IB, et al. Widespread positive selection in synonymous sites of mammalian genes. *Mol Biol Evol* 2007 Aug;24(8):1821e31.
- [72] Wang D, Sadee W. Searching for polymorphisms that affect gene expression and mRNA processing: example ABCB1 (MDR1). *AAPS J* 2006;8(3):E515e20.
- [73] Defesche JC, Schuurman EJ, Klaijns LN, Khoo KL, Wiegman A, Stalenhoef AF. Silent exonic mutations in the low-density lipoprotein receptor gene that cause familial hypercholesterolemia by affecting mRNA splicing. *Clin Genet* 2008 Jun;73(6):573e8.
- [74] Livingstone M, Atas E, Meller A, Sonenberg N. Mechanisms governing the control of mRNA translation. *Phys Biol* 2010;7(2):021001.

- [75] Mazumder B, Seshadri V, Fox PL. Translational control by the 30-UTR: the ends specify the means. *Trends Biochem Sci* 2003 Feb;28(2):91e8.
- [76] Mishra PJ, Humeniuk R, Longo-Sorbello GS, Banerjee D, Bertino JR. A miR-24 microRNA binding-site polymorphism in dihydrofolate reductase gene leads to methotrexate resistance. *Proc Natl Acad Sci U S A* 2007 Aug 14;104(33):13513e18.
- [77] Vikman S, Brena RM, Armstrong P, Hartiala J, Stephensen CB, Allayee H. Functional analysis of 5-lipoxygenase promoter repeat variants. *Hum Mol Genet* 2009 Dec 1;18(23):4521e9.
- [78] Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med* 2004 Jan 1;350(1):29e37.
- [79] Parle-McDermott A, Pangilinan F, O'Brien KK, Mills JL, Magee AM, Troendle J, et al. A common variant in MTHFD1L is associated with neural tube defects and mRNA splicing efficiency. *Hum Mutat* 2009 Dec;30(12):1650e6.
- [80] Sudmant PH, Kitzman JO, Antonacci F, Alkan C, Malig M, Tsalenko A, et al. Diversity of human copy number variation and multicopy genes. *Science* 2010 Oct 29;330(6004):641e6.
- [81] Stamoulis C, Betensky RA. A novel signal processing approach for the detection of copy-number variations in the human genome. *Bioinformatics* 2011 Jul 12.
- [82] Varma V, Wise C, Kaput J. Carbohydrate metabolic pathway genes associated with quantitative trait loci (QTL) for obesity and type 2 diabetes: identification by data mining. *Biotechnol J* 2010 Sep;5(9):942e9.
- [83] Sindi SS, Raphael BJ. Identification and frequency estimation of inversion polymorphisms from haplotype data. *J Comput Biol* 2010 Mar;17(3):517e31.
- [84] Naylor JA, Nicholson P, Goodeve A, Hassock S, Peake I, Giannelli F. A novel DNA inversion causing severe hemophilia A. *Blood* 1996 Apr 15;87(8):3255e61.
- [85] Yamaguchi-Kabata Y, Shimada MK, Hayakawa Y, Minoshima S, Chakraborty R, Gojobori T, et al. Distribution and effects of nonsense polymorphisms in human genes. *PLoS One* 2008;3(10):e3393.
- [86] Gordon N. Ornithine transcarbamylase deficiency: a urea cycle defect. *Eur J Paediatr Neurol* 2003;7(3):115e21.
- [87] Blau N, Scherer-Oppliger T, Baumer A, Riegel M, Matasovic A, Schinzel A, et al. Isolated central form of tetrahydrobiopterin deficiency associated with hemizygoty on chromosome 11q and a mutant allele of PTPS. *Hum Mutat* 2000;16(1):54e60.
- [88] Roudnitzky N, Bufe B, Thalmann S, Kuhn C, Gunn HC, Xing C, et al. Genomic, genetic and functional dissection of bitter taste responses to artificial sweeteners. *Hum Mol Genet* 2011 Sep 1;20(17):3437e49.
- [89] Hosking FJ, Papaemmanuil E, Sheridan E, Kinsey SE, Lightfoot T, Roman E, et al. Genome-wide homozygosity signatures and childhood acute lymphoblastic leukemia risk. *Blood* 2010 Jun 3;115(22):4472e7.
- [90] Martin DI, Cropley JE, Suter CM. Epigenetics in disease: Leader or follower? *Epigenetics* 2011 Jul 1;6(7):843e8.
- [91] Hitchins M, Owens S, Kwok CT, Godsmark G, Algar U, Ramesar R. Identification of new cases of early-onset colorectal cancer with an MLH1 epimutation in an ethnically diverse South African cohort(dagger). *Clin Genet* 2011 Nov;80(5):428e34.
- [92] Shibui T, Higo Y, Tsutsui TW, Uchida M, Oshimura M, Barrett JC, et al. Changes in expression of imprinted genes following treatment of human cancer cell lines with non-mutagenic or mutagenic carcinogens. *Int J Oncol* 2008 Aug;33(2):351e60.

BÖLÜM 3

Nutrigenetik Farklılıklar Nereden Gelmektedir?

TERİMLER

- Kurucu etki: Birkaç atadan gelen nüfus genişlemesi bazı yaygın varyantları açıklayabilir.
- Homininler: İnsan türleri (Homo sapiens, Homo ergaster ve Homo rudolfenis) ve yakın zamandaki ataları.
- Hominoidler: Homininler artı orangutanlar, goriller ve şempanzeler.
- Nutritope: Belirli bir besin ögesi bolluğu ve besin toksinleri içeren çevre.
- Pleiotropik: Farklı ve ilgisiz vücudu ilgilendiren bir etki tanımlamak fonksiyonlar.
- Psödojen: Fonksiyonel bir genden alçalma ile türetilmiş fonksiyonel olmayan genomik dizi

ÖZET

İnsanların beslenme gereksinimleri, çağlar boyunca gelişmiştir. Erken primat ataları esas olarak meyve ve yaprak tüketerek yaşadılar. Daha sonraki bazı atalar nişastalı kökleri ve çim tohumlarını yemeyi öğrendi ve diğerleri av hayvan etleri ve balıklarla hayatta kaldılar. Tarım, mayalama, sığır sürüsü ve yemek pişirme yeni besin öğeleri kaynakları oluşturdu. Tüm bu gelişmeler izlerini genomumuza bıraktılar. Spesifik besin öğelerini sindirme ve metabolize etme konusundaki çeşitli yeteneklerimiz, çok farklı beslenme ortamlarının (nutritoplar) yankılarıdır. Besinlerden C vitamini bağımlılığımız, meyve ve yaprakların bol olduğu zamanlara geri döner, ancak bugün herkesin aynı miktarlara ihtiyacı yoktur. Bazı popülasyonlar, dünyanın diğer bölgelerindeki insanların hayatta kalabilmesi için düşük alım seviyelerine uyum sağlamıştır. Bazılarımız rahatsızlık duymadan çok süt içebiliriz; diğerleri karın ağrısı ve hafif miktarlarda bile şişkinlik çekerler. Birçok kişi alkollü içecekler içerken sarhoş olur ve ancak daha sonra akşamdan kalma olur. Diğerleri ise akşamdan kalma belirtilerini yüksek ruhlular sarhoşluk yolunda çok az hisseder. Bu farklılıklar nereden geliyor ve nasıl çalışıyor? Bu bölüm genomumuzu şekillendiren beslenme

akşamdan kalma gibi bir şey yaşar. Belirli besin ve besin öğelerine farklı tepkilerin başka örnekleri çoktur. Kendi genetik varyant setimiz hepimizi benzersiz kılıyor ve bize kişisel bir beslenme dozu ve yapmama şekli veriyor.

Şimdi, bu örnekler anlatmak için ilginç olabilir, ama sadece birkaç fıkradan daha fazlası mı? Bir sonraki bölüm, bireysel genetik yatkınlığın birçok besin öğesinin metabolizmasını nasıl etkilediğini daha sistematik olarak gözden geçirecektir.

KAYNAKLAR

- [1] Morris JG. Idiosyncratic nutrient requirements of cats appear to be diet-induced evolutionary adaptations. *Nutr Res Rev* 2002;15(1):153e68.
- [2] Sanderson SL, Gross KL, Ogburn PN, Calvert C, Jacobs G, Lowry SR, et al. Effects of dietary fat and L-carnitine on plasma and whole blood taurine concentrations and cardiac function in healthy dogs fed protein-restricted diets. *Am J Vet Res* 2001;62(10):1616e23.
- [3] Rebouche CJ, Lombard KA, Chenard CA. Renal adaptation to dietary carnitine in humans. *Am J Clin Nutr* 1993;58(5):660e5.
- [4] Pollock JI, Mullin RJ. Vitamin C biosynthesis in prosimians: evidence for the anthropoid affinity of Tarsius. *Am J Phys Anthropol* 1987;73(1):65e70.
- [5] Cui J, Pan YH, Zhang Y, Jones G, Zhang S. Progressive pseudogenization: vitamin C synthesis and its loss in bats. *Mol Biol Evol* 2011;28(2):1025e31.
- [6] Nishikimi M, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. *Am J Clin Nutr* 1991;54(Suppl. 6):1203Se8S.
- [7] Inai Y, Ohta Y, Nishikimi M. The whole structure of the human nonfunctional L-gulonolactone oxidase gene and the evolution of repetitive sequences thereon. *J Nutr Sci Vitaminol (Tokyo)* 2003;49(5):315e19.
- [8] Burge CB, Karlin S. Finding the genes in genomic DNA. *Curr Opin Struct Biol* 1998;8(3):346e54.
- [9] Horwitt MK, Harper AE, Henderson LM. Niacin-tryptophan relationships for evaluating niacin equivalents. *Am J Clin Nutr* 1981;34(3):423e7.
- [10] Tanaka T, Tateno Y, Gojobori T. Evolution of vitamin B6 (pyridoxine) metabolism by gain and loss of genes. *Mol Biol Evol* 2005;22(2):243e50.
- [11] Hrdlickova B, Westra HJ, Franke L, Wijmenga C. Celiac disease: moving from genetic associations to causal variants. *Clin Genet* 2011 Sep;80(3):203e313.
- [12] Mountain JL, Cavalli-Sforza LL. Inference of human evolution through cladistic analysis of nuclear DNA restriction polymorphisms. *Proc Natl Acad Sci U S A* 1994;91(14):6515e19.
- [13] Sørensen Thorvald. Some ecosystemal characteristics determined by Raunkjær's circling method. Helsinki: Skandinaviska naturforskaremöten; 1936. pp. 474e475.
- [14] Sponheimer M, Codron D, Passey BH, de Ruiter DJ, Cerling TE, Lee-Thorp JA. Using carbon isotopes to track dietary change in modern, historical, and ancient primates. *Am J Phys Anthropol* 2009;140(4):661e70.
- [15] Fuller BT, Marquez-Grant N, Richards MP. Investigation of diachronic dietary patterns on the islands of Ibiza and Formentera, Spain: Evidence from carbon and nitrogen stable isotope ratio analysis. *Am J Phys Anthropol* 2010;143(4):512e22.
- [16] Oelze VM, Fuller BT, Richards MP, Fruth B, Surbeck M, Hublin JJ, et al. Exploring the contribution and significance of animal protein in the diet of bonobos by stable isotope ratio analysis of hair. *Proc Natl Acad Sci U S A* 2011;108(24):9792e7.
- [17] Teaford MF, Ungar PS. Diet and the evolution of the earliest human ancestors. *Proc Natl Acad Sci U S A* 2000;97(25):13506e11.
- [18] Laden G, Wrangham R. The rise of the hominids as an adaptive shift in fallback foods: plant underground storage organs (USOs) and australopithecine origins. *J Hum Evol* 2005;49(4): 482e98.

- [19] Luca F, Perry GH, Di Rienzo A. Evolutionary adaptations to dietary changes. *Annu Rev Nutr* 2010;30:291e314.
- [20] Organ C, Nunn CL, Machanda Z, Wrangham RW. Phylogenetic rate shifts in feeding time during the evolution of Homo. *Proc Natl Acad Sci U S A* 2011;108(35):14555e9.
- [21] Matthews LJ, Butler PM. Novelty-seeking DRD4 polymorphisms are associated with human migration distance out-of-Africa after controlling for neutral population gene structure. *Am J Phys Anthropol* 2011;145(3):382e9.
- [22] Balter V, Simon L. Diet and behavior of the Saint-Cesaire Neanderthal inferred from biogeochemical data inversion. *J Hum Evol* 2006;51(4):329e38.
- [23] Yotova V, Lefebvre JF, Moreau C, Gbeha E, Hovhannesian K, Bourgeois S, et al. An X-linked haplotype of neandertal origin is present among all non-African populations. *Mol Biol Evol* 2011;28(7):1957e62.
- [24] Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, et al. Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature* 2010;468(7327): 1053e60.
- [25] Le Bras-Goude G, Binder D, Zemor A, Richards MP. New radiocarbon dates and isotope analysis of Neolithic human and animal bone from the Fontbregoua Cave (Salernes, Var, France). *J Anthropol Sci* 2010;88:167e78.
- [26] Macko SA, Engel MH, Andrusevich V, Lubec G, O'Connell TC, Hedges RE. Documenting the diet in ancient human populations through stable isotope analysis of hair. *Philos Trans R Soc Lond B Biol Sci* 1999;354(1379):65e75.
- [27] Holden TG. *The Food Remains from the Colon of the Tyrolean Ice Man*. Oxford, England: Oxbow Books; 2002.
- [28] Porsild A. Edible plants of the Arctic. *Arctic* 1953;6:15e34.
- [29] Milman N, Laursen J, Mulvad G, Pedersen HS, Pedersen AN, Saaby H. ¹³Carbon and ¹⁵nitrogen isotopes in autopsy liver tissue samples from Greenlandic Inuit and Danes: consumption of marine versus terrestrial food. *Eur J Clin Nutr* 2010;64(7):739e44.
- [30] Naughton JM, O'Dea K, Sinclair AJ. Animal foods in traditional Australian aboriginal diets: polyunsaturated and low in fat. *Lipids* 1986;21(11):684e90.
- [31] O'Dea K. Traditional diet and food preferences of Australian aboriginal hunter-gatherers. *Philos Trans R Soc Lond B Biol Sci* 1991;334(1270):233e40. discussion, 40e1.
- [32] O'Dea K, White NG, Sinclair AJ. An investigation of nutrition-related risk factors in an isolated Aboriginal community in northern Australia: advantages of a traditionally-orientated life-style. *Med J Aust* 1988;148(4):177e80.
- [33] Thorburn AW, Brand JC, Truswell AS. Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes? *Am J Clin Nutr* 1987;45(1): 98e106.
- [34] O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian aborigines after temporary reversion to traditional lifestyle. *Diabetes* 1984;33(6):596e603.
- [35] Lokki AI, Jarvela I, Israelsson E, Maiga B, Troye-Blomberg M, Dolo A, et al. Lactase persistence genotypes and malaria susceptibility in Fulani of Mali. *Malar J* 2011;10:9.
- [36] Burger J, Kirchner M, Bramanti B, Haak W, Thomas MG. Absence of the lactase-persistence-associated allele in early Neolithic Europeans. *Proc Natl Acad Sci U S A* 2007;104(10): 3736e41.
- [37] Gerbault P, Liebert A, Itan Y, Powell A, Currat M, Burger J, et al. Evolution of lactase persistence: an example of human niche construction. *Philos Trans R Soc Lond B Biol Sci* 2011;366(1566):863e77.
- [38] Evershed RP, Payne S, Sherratt AG, Copley MS, Coolidge J, Urem-Kotsu D, et al. Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding. *Nature* 2008;455(7212):528e31.
- [39] Copley MS, Berstan R, Dudd SN, Docherty G, Mukherjee AJ, Straker V, et al. Direct chemical evidence for widespread dairying in prehistoric Britain. *Proc Natl Acad Sci U S A* 2003; 100(4):1524e9.

- [40] Campbell CD, Ogburn EL, Lunetta KL, Lyon HN, Freedman ML, Groop LC, et al. Demonstrating stratification in a European American population. *Nat Genet* 2005;37(8): 868e72.
- [41] Waud JP, Matthews SB, Campbell AK. Measurement of breath hydrogen and methane, together with lactase genotype, defines the current best practice for investigation of lactose sensitivity. *Ann Clin Biochem* 2008;45(Pt 1):50e8.
- [42] Xu L, Sun H, Zhang X, Wang J, Sun D, Chen F, et al. The -22018A allele matches the lactase persistence phenotype in northern Chinese populations. *Scand J Gastroenterol* 2010;45(2): 168e74.
- [43] Heyer E, Brazier L, Segurel L, Hegay T, Austerlitz F, Quintana-Murci L, et al. Lactase persistence in central Asia: phenotype, genotype, and evolution. *Human Biology* 2011;83(3): 379e92.
- [44] Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. *BMC Evol Biol* 2010;10:36.
- [45] Rahimi AG, Delbruck H, Haeckel R, Goedde HW, Flatz G. Persistence of high intestinal lactase activity (lactose tolerance) in Afghanistan. *Hum Genet* 1976;34(1):57e62.
- [46] Gallego Romero I, Basu Mallick C, Liebert A, Crivellaro F, Chaubey G, Itan Y, et al. Herders of Indian and European cattle share their predominant allele for lactase persistence. *Mol Biol Evol* 2012 Jan;29(1):249e60.
- [47] Peng MS, He JD, Zhu CL, Wu SF, Jin JQ, Zhang YP. Lactase persistence may have an independent origin in Tibetan populations from Tibet, China. *J Human Genet* 2012 Jun;57(6): 394e7.
- [48] Ingram CJ, Raga TO, Tarekegn A, Browning SL, Elamin MF, Bekele E, et al. Multiple rare variants as a cause of a common phenotype: several different lactase persistence associated alleles in a single ethnic group. *J Mol Evol* 2009;69(6):579e88.
- [49] Tishkoff SA, Reed FA, Ranciaro A, Voight BF, Babbitt CC, Silverman JS, et al. Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet* 2007;39(1): 31e40.
- [50] Mulcare CA, Weale ME, Jones AL, Connell B, Zeitlyn D, Tarekegn A, et al. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. *Am J Hum Genet* 2004;74(6):1102e10.
- [51] Ingram CJ, Elamin MF, Mulcare CA, Weale ME, Tarekegn A, Raga TO, et al. A novel polymorphism associated with lactose tolerance in Africa: multiple causes for lactase persistence? *Hum Genet* 2007;120(6):779e88.
- [52] Khabarova Y, Torniaainen S, Savilahti E, Isokoski M, Mattila K, Jarvela I. The -13914G>A variant upstream of the lactase gene (LCT) is associated with lactase persistence/ non-persistence. *Scand J Clin Lab Invest* 2010;70(5):354e7.
- [53] Torniaainen S, Parker MI, Holmberg V, Lahtela E, Dandara C, Jarvela I. Screening of variants for lactase persistence/non-persistence in populations from South Africa and Ghana. *BMC Genet* 2009;10:31.
- [54] Jensen TG, Liebert A, Lewinsky R, Swallow DM, Olsen J, Troelsen JT. The -14010*C variant associated with lactase persistence is located between an Oct-1 and HNF1alpha binding site and increases lactase promoter activity. *Hum Genet* 2011 Oct;130(4):483e93.
- [55] Mattar R, Monteiro Mdo S, Silva JM, Carrilho FJ. LCT-22018G>A single nucleotide polymorphism is a better predictor of adult-type hypolactasia/lactase persistence in Japanese- Brazilians than LCT-13910C<T. *Clinics (Sao Paulo)* 2010;65(12):1399.
- [56] Nemeth K, Plumb GW, Berrin JG, Juge N, Jacob R, Naim HY, et al. Deglycosylation by small intestinal epithelial cell beta-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. *Eur J Nutr* 2003;42(1):29e42.
- [57] Perry GH, Dominy NJ, Claw KG, Lee AS, Fiegler H, Redon R, et al. Diet and the evolution of human amylase gene copy number variation. *Nat Genet* 2007;39(10):1256e60.
- [58] Mandel AL, Peyrot des Gachons C, Plank KL, Alarcon S, Breslin PA. Individual differences in AMY1 gene copy number, salivary alpha-amylase levels, and the perception of oral starch. *PLoS One* 2010;5(10):e13352.

- [59] Ferry AL, Mitchell JR, Hort J, Hill SE, Taylor AJ, Lagarrigue S, et al. In-mouth amylase activity can reduce perception of saltiness in starch-thickened foods. *J Agric Food Chem* 2006;54(23): 8869e73.
- [60] de Wijk RA, Prinz JF, Engelen L, Weenen H. The role of alpha-amylase in the perception of oral texture and flavour in custards. *Physiol Behav* 2004;83(1):81e91.
- [61] Mandel AL, Breslin PA. High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. *J Nutr* 2012;142(5): 853e8.
- [62] Husemoen LL, Jorgensen T, Borch-Johnsen K, Hansen T, Pedersen O, Linneberg A. The association of alcohol and alcohol metabolizing gene variants with diabetes and coronary heart disease risk factors in a white population. *PLoS One* 2010;5(8):e11735.
- [63] Ginsberg G, Smolenski S, Neafsey P, Hattis D, Walker K, Guyton KZ, et al. The influence of genetic polymorphisms on population variability in six xenobiotic-metabolizing enzymes. *J Toxicol Environ Health B Crit Rev* 2009;12(5e6):307e33.
- [64] Peng Y, Shi H, Qi XB, Xiao CJ, Zhong H, Ma RL, et al. The ADH1B Arg47His polymorphism in east Asian populations and expansion of rice domestication in history. *BMC Evol Biol* 2010;10:15.
- [65] Li D, Zhao H, Gelernter J. Strong association of the alcohol dehydrogenase 1B gene (ADH1B) with alcohol dependence and alcohol-induced medical diseases. *Biol Psychiatry* 2011;70(6):504e12.
- [66] Li H, Gu S, Cai X, Speed WC, Pakstis AJ, Golub EI, et al. Ethnic related selection for an ADH Class I variant within East Asia. *PLoS One* 2008;3(4):e1881.
- [67] Homann N, Stickel F, König IR, Jacobs A, Junghanns K, Benesova M, et al. Alcohol dehydrogenase 1C*1 allele is a genetic marker for alcohol-associated cancer in heavy drinkers. *Int J Cancer* 2006;118(8):1998e2002.
- [68] Eriksson CJ. The role of acetaldehyde in the actions of alcohol (update 2000). *Alcohol Clin Exp Res* 2001;25(Suppl. 5 ISBRA):15Se32S.
- [69] Shibuya A, Yoshida A. Frequency of the atypical aldehyde dehydrogenase-2 gene (ALDH2(2)) in Japanese and Caucasians. *Am J Hum Genet* 1988;43(5):741e3.
- [70] Takeshita T, Morimoto K. Self-reported alcohol-associated symptoms and drinking behavior in three ALDH2 genotypes among Japanese university students. *Alcohol Clin Exp Res* 1999;23(6):1065e9.
- [71] Fischer M, Wetherill LF, Carr LG, You M, Crabb DW. Association of the aldehyde dehydrogenase 2 promoter polymorphism with alcohol consumption and reactions in an American Jewish population. *Alcohol Clin Exp Res* 2007;31(10):1654e9.
- [72] Wilmshurst JM, Hunt TL, Lipo CP, Anderson AJ. High-precision radiocarbon dating shows recent and rapid initial human colonization of East Polynesia. *Proc Natl Acad Sci U S A* 2011;108(5):1815e20.
- [73] Finney BR. Voyaging canoes and the settlement of Polynesia. *Science* 1977;196(4296): 1277e85.
- [74] Fitzpatrick S, Callaghan R. Magellan's crossing of the Pacific. *The Journal of Pacific History* 2008;43(2):145e65.
- [75] Nagel R, Etcheverry R, Guzman C. Haptoglobin Types in Inhabitants of Easter Island. *Nature* 1964;201:216e7.
- [76] Melamed-Frank M, Lache O, Enav BI, Szafranek T, Levy NS, Ricklis RM, et al. Structure-function analysis of the antioxidant properties of haptoglobin. *Blood* 2001;98(13): 3693e8.
- [77] Langlois MR, Delanghe JR, De Buyzere ML, Bernard DR, Ouyang J. Effect of haptoglobin on the metabolism of vitamin C. *Am J Clin Nutr* 1997;66(3):606e10.
- [78] De Bacquer D, De Backer G, Langlois M, Delanghe J, Kesteloot H, Kornitzer M. Haptoglobin polymorphism as a risk factor for coronary heart disease mortality. *Atherosclerosis* 2001;157(1):161e6.
- [79] Tye-Din JA, Stewart JA, Dromey JA, Beissbarth T, van Heel DA, Tatham A, et al. Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease. *Sci Transl Med* 2010;2(41):.41ra51.

- [80] Caja S, Maki M, Kaukinen K, Lindfors K. Antibodies in celiac disease: implications beyond diagnostics. *Cell Mol Immunol* 2011;8(2):103e9.
- [81] Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. *Aliment Pharmacol Ther* 2012 Mar;35(5): 540e51.
- [82] Welander A, Prutz KG, Foröd M, Ludvigsson JF. Increased risk of end-stage renal disease in individuals with coeliac disease. *Gut* 2012;61(1):64e8.
- [83] Sainsbury A, Sanders DS, Ford AC. Meta-analysis: coeliac disease and hypertransaminasaemia. *Aliment Pharmacol Ther* 2011 Jul;34(1):33e40.
- [84] Walker MM, Murray JA, Ronkainen J, Aro P, Storskrubb T, D'Amato M, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. *Gastroenterology* 2010;139(1):112e9.
- [85] Mones RL, Yankah A, Duelfer D, Bustami R, Mercer G. Disaccharidase deficiency in pediatric patients with celiac disease and intact villi. *Scand J Gastroenterol* 2011;46(12): 1429e34.
- [86] Sperandeo MP, Tosco A, Izzo V, Tucci F, Troncone R, Auricchio R, et al. Potential celiac patients: a model of celiac disease pathogenesis. *PLoS One* 2011;6(7):e21281.
- [87] Biagi F, Bianchi PI, Vattiato C, Marchese A, Trotta L, Badulli C, et al. Influence of HLA-DQ2 and DQ8 on severity in celiac disease. *J Clin Gastroenterol* 2012;46(1):46e50.
- [88] Trynka G, Hunt KA, Bockett NA, Romanos J, Mistry V, Szperl A, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet* 2011;43(12):1193e201.
- [89] Pascolo P, Faleschini E, Tonini G, Ventura A. Type 1 diabetes mellitus and celiac disease: usefulness of gluten-free diet. *Acta Diabetol* 2011 [Epub ahead of print].
- [90] Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;371(9606):64e74.
- [91] Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. *Baillieres Best Pract Res Clin Haematol* 2000;13(1):21e38.
- [92] Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis* 2009;42(3):267e78.
- [93] Hedrick PW. Population genetics of malaria resistance in humans. *Heredity* 2011 Oct;107(4): 283e304.
- [94] McMillan DC, Schey KL, Meier GP, Jollow DJ. Chemical analysis and hemolytic activity of the fava bean aglycon divicine. *Chem Res Toxicol* 1993;6(4):439e44.
- [95] Brandt O, Rieger A, Geusau A, Stingl G. Peas, beans, and the Pythagorean theorem: the relevance of glucose-6-phosphate dehydrogenase deficiency in dermatology. *J Dtsch Dermatol Ges* 2008;6(7):534e9.
- [96] Chango A, Abdennebi-Najar L. Folate metabolism pathway and *Plasmodium falciparum* malaria infection in pregnancy. *Nutr Rev* 2011;69(1):34e40.
- [97] Asawamahsakda W, Yuthavong Y. The methionine synthesis cycle and salvage of methyl-tetrahydrofolate from host red cells in the malaria parasite (*Plasmodium falciparum*). *Parasitology* 1993;107(Pt 1):1e10.
- [98] Wilcken B, Bamforth F, Li Z, Zhu H, Ritvanen A, Renlund M, et al. Geographical and ethnic variation of the 677C>T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): findings from over 7000 newborns from 16 areas world wide. *J Med Genet* 2003;40(8): 619e25.
- [99] Thiagarajah JR, Verkman AS. New drug targets for cholera therapy. *Trends Pharmacol Sci* 2005;26(4):172e5.
- [100] Sonawane ND, Hu J, Muanprasat C, Verkman AS. Luminally active, nonabsorbable CFTR inhibitors as potential therapy to reduce intestinal fluid loss in cholera. *FASEB J* 2006;20(1): 130e2.
- [101] van de Vosse E, Ali S, de Visser AW, Surjadi C, Widjaja S, Vollaard AM, et al. Susceptibility to typhoid fever is associated with a polymorphism in the cystic fibrosis transmembrane conductance regulator (CFTR). *Hum Genet* 2005;118(1):138e40.

- [102] Dean M, Carrington M, O'Brien SJ. Balanced polymorphism selected by genetic versus infectious human disease. *Annu Rev Genomics Hum Genet* 2002;3:263e92.
- [103] Cohen-Cymberek M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med* 2011;183(11):1463e71.
- [104] Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros* 2011;10(Suppl. 2):S86e102.
- [105] Sathe MN, Patel AS. Update in pediatrics: focus on fat-soluble vitamins. *Nutr Clin Pract* 2010;25(4):340e6.
- [106] Liu P, Shah BP, Croasdell S, Gilbertson TA. Transient receptor potential channel type M5 is essential for fat taste. *J Neurosci* 2011;31(23):8634e42.
- [107] Galindo MM, Voigt N, Stein J, van Lengerich J, Raguse JD, Hofmann T, et al. G protein-coupled receptors in human fat taste perception. *Chem Senses* 2012 Feb;37(2): 123e39.
- [108] Ming D, Ninomiya Y, Margolskee RF. Blocking taste receptor activation of gustducin inhibits gustatory responses to bitter compounds. *Proc Natl Acad Sci U S A* 1999;96(17): 9903e8.
- [109] Kamei K, Takano R, Miyasaka A, Imoto T, Hara S. Amino acid sequence of sweet-taste-suppressing peptide (gurmarin) from the leaves of *Gymnema sylvestre*. *J Biochem* 1992;111(1):109e12.
- [110] Yasumatsu K, Ohkuri T, Sanematsu K, Shigemura N, Katsukawa H, Sako N, et al. Genetically-increased taste cell population with G(alpha)-gustducin-coupled sweet receptors is associated with increase of gurmarin-sensitive taste nerve fibers in mice. *BMC Neurosci* 2009;10:152.
- [111] Kojima I, Nakagawa Y. The role of the sweet taste receptor in enteroendocrine cells and pancreatic beta-cells. *Diabetes Metab J* 2011;35(5):451e7.
- [112] Finger TE, Kinnamon SC. Taste isn't just for taste buds anymore. *F1000 Biol Rep* 2011;3:20.
- [113] Iguchi N, Ohkuri T, Slack JP, Zhong P, Huang L. Sarco/endoplasmic reticulum Ca-ATPases (SERCA) contribute to GPCR-mediated taste perception. *PLoS One* 2011;6(8):23165.
- [114] Kim U, Wooding S, Ricci D, Jorde LB, Drayna D. Worldwide haplotype diversity and coding sequence variation at human bitter taste receptor loci. *Hum Mutat* 2005;26(3):199-204.
- [115] Reed DR, Zhu G, Breslin PA, Duke FF, Henders AK, Campbell MJ, et al. The perception of quinine taste intensity is associated with common genetic variants in a bitter receptor cluster on chromosome 12. *Hum Mol Genet* 2010;19(21):4278-85.
- [116] Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. Genetic variation in taste perception: does it have a role in healthy eating? *Proc Nutr Soc* 2011;70(1):135-43.
- [117] Sacerdote C, Guarrera S, Smith GD, Grioni S, Krogh V, Masala G, et al. Lactase persistence and bitter taste response: instrumental variables and Mendelian randomization in epidemiologic studies of dietary factors and cancer risk. *Am J Epidemiol* 2007;166(5):576-81.
- [118] Duffy VB, Hayes JE, Davidson AC, Kidd JR, Kidd KK, Bartoshuk LM. Vegetable intake in college-aged adults is explained by oral sensory phenotypes and TAS2R38 genotype. *Chemosens Percept* 2010;3(3e4):137-48.
- [119] Lalueza-Fox C, Gigli E, de la Rasilla M, Fortea J, Rosas A. Bitter taste perception in Neanderthals through the analysis of the TAS2R38 gene. *Biol Lett* 2009;5(6):809-11.
- [120] Wooding S, Gunn H, Ramos P, Thalmann S, Xing C, Meyerhof W. Genetics and bitter taste responses to goitrin, a plant toxin found in vegetables. *Chem Senses* 2010;35(8):685-92.
- [121] Roudnitzky N, Bufe B, Thalmann S, Kuhn C, Gunn HC, Xing C, et al. Genomic, genetic and functional dissection of bitter taste responses to artificial sweeteners. *Hum Mol Genet* 2011;20(17):3437-49.
- [122] Li X, Li W, Wang H, Bayley DL, Cao J, Reed DR, et al. Cats lack a sweet taste receptor. *J Nutr* 2006;136(Suppl. 7):1932S-4S.
- [123] Li X, Glaser D, Li W, Johnson WE, O'Brien SJ, Beauchamp GK, et al. Analyses of sweet receptor gene (*Tas1r2*) and preference for sweet stimuli in species of Carnivora. *J Hered* 2009;100(Suppl. 1): S90-100.

- [124] Sakurai T, Misaka T, Ueno Y, Ishiguro M, Matsuo S, Ishimaru Y, et al. The human bitter taste receptor, hTAS2R16, discriminates slight differences in the configuration of disaccharides. *Biochem Biophys Res Commun* 2010;402(4):595-601.
- [125] Bachmanov AA, Bosak NP, Floriano WB, Inoue M, Li X, Lin C, et al. Genetics of sweet taste preferences. *Flavour Fragr J* 2011;26(4):286-94.
- [126] Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. Alelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. *Curr Biol* 2009;19(15):1288-93.
- [127] Eny KM, Wolever TM, Corey PN, El-Soheby A. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. *Am J Clin Nutr* 2010;92(6):1501-10.
- [128] Fushan AA, Simons CT, Slack JP, Drayna D. Association between common variation in genes encoding sweet taste signaling components and human sucrose perception. *Chem Senses* 2010;35(7):579-92.
- [129] Shigemura N, Shirosaki S, Sanematsu K, Yoshida R, Ninomiya Y. Genetic and molecular basis of individual differences in human umami taste perception. *PLoS One* 2009;4(8): 6717.
- [130] Raliou M, Grauso M, Hoffmann B, Schlegel-Le-Poupon C, Nespoulous C, Debat H, et al. Human genetic polymorphisms in T1R1 and T1R3 taste receptor subunits affect their function. *Chem Senses* 2011;36(6):527-37.
- [131] Chen QY, Alarcon S, Tharp A, Ahmed OM, Estrella NL, Greene TA, et al. Perceptual variation in umami taste and polymorphisms in TAS1R taste receptor genes. *Am J Clin Nutr* 2009;90(3):770S-9S.
- [132] Ichise T, Kano M, Hashimoto K, Yanagihara D, Nakao K, Shigemoto R, et al. mGluR1 in cerebellar Purkinje cells essential for long-term depression, synapse elimination, and motor coordination. *Science* 2000;288(5472):1832-5.
- [133] Simon L, Toth J, Molnar L, Agoston DV. MRI analysis of mGluR5 and mGluR1 antagonists, MTEP and R214127 in the cerebral forebrain of awake, conscious rats. *Neurosci Lett* 2011;505(2):155-9.
- [134] Sun H, Neugebauer V. mGluR1, but not mGluR5, activates feed-forward inhibition in the medial prefrontal cortex to impair decision making. *J Neurophysiol* 2011;106(2): 960-73.
- [135] Downey PM, Petro R, Simon JS, Devlin D, Lozza G, Veltri A, et al. Identification of single nucleotide polymorphisms of the human metabotropic glutamate receptor 1 gene and pharmacological characterization of a P993S variant. *Biochem Pharmacol* 2009;77(7): 1246-53.
- [136] Zhao H, Yang JR, Xu H, Zhang J. Pseudogenization of the umami taste receptor gene *Tas1r1* in the giant panda coincided with its dietary switch to bamboo. *Mol Biol Evol* 2010;27(12): 2669-73.
- [137] Martin C, Passilly-Degrace P, Gaillard D, Merlin JF, Chevrot M, Besnard P. The lipid-sensor candidates CD36 and GPR120 are differentially regulated by dietary lipids in mouse taste buds: impact on spontaneous fat preference. *PLoS One* 2011;6(8):24014.
- [138] Keller KL, Liang LC, Sakimura J, May D, van Belle C, Breen C, et al. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in african americans. *Obesity (Silver Spring)* 2012 May;20(5):1066-73.
- [139] Pepino MY, Love-Gregory L, Klein S, Abumrad NA. The fatty acid translocase gene, CD36, and lingual lipase influence oral sensitivity to fat in obese subjects. *J Lipid Res* 2012 Mar;53(3):561-6.
- [140] Wise PM, Hansen JL, Reed DR, Breslin PA. Twin study of the heritability of recognition thresholds for sour and salty taste. *Chem Senses* 2007;32(8):749-54.
- [141] Ayya N, Beauchamp GK. Short-term effects of diet on salt taste preference. *Appetite* 1992; 18(1):77-82.
- [142] Stein LJ, Cowart BJ, Epstein AN, Pilot LJ, Laskin CR, Beauchamp GK. Increased liking for salty foods in adolescents exposed during infancy to a chloride-deficient feeding formula. *Appetite* 1996;27(1):65-77.

- [143] Amoore J, Forrester L. Anosmia to trimethylamine: The primary fishy odor. *J Chem Ecol* 1976;2:49-56.
- [144] Rehman HU. Fish odor syndrome. *Postgrad Med J* 1999;75(886):451-2.
- [145] Menashe I, Man O, Lancet D, Gilad Y. Different noses for different people. *Nat Genet* 2003;34(2):143-4.
- [146] Hasin Y, Olender T, Khen M, Gonzaga-Jauregui C, Kim PM, Urban AE, et al. High-resolution copy-number variation map reflects human olfactory receptor diversity and evolution. *PLoS Genet* 2008;4(11):1000249.
- [147] Waring RH, Mitchell SC, Fenwick GR. The chemical nature of the urinary odour produced by man after asparagus ingestion. *Xenobiotica* 1987;17(11):1363-71.
- [148] Pelchat ML, Bykowski C, Duke FF, Reed DR. Excretion and perception of a characteristic odor in urine after asparagus ingestion: a psychophysical and genetic study. *Chem Senses* 2011;36(1):9-17.
- [149] Eriksson N, Macpherson JM, Tung JY, Hon LS, Naughton B, Saxonov S, et al. Web-based, participant-driven studies yield novel genetic associations for common traits. *PLoS Genet* 2010;6(6):1000993.
- [150] Borrud LG, Flegal KM, Looker AC, Everhart JE, Harris TB, Shepherd JA. Body composition data for individuals 8 years of age and older: US population, 1999e2004. *Vital Health Stat* 2010;11(250):1-87.
- [151] Dasilva SG, Guidetti L, Buzzachera CF, Elsangedy HM, Krinski K, De Campos W, et al. Gender-based differences in substrate use during exercise at a self-selected pace. *J Strength Cond Res* 2011;25(9):2544-51.
- [152] Voorhoeve PG, van Mechelen W, Uitterlinden AG, Deleamarre-van de Waal HA, Lamberts SW. Estrogen receptor-alpha gene polymorphisms and body composition in children and adolescents. *Horm Res Paediatr* 2011;76(2):86-92.
- [153] da Costa KA, Kozyreva OG, Song J, Galanko JA, Fischer LM, Zeisel SH. Common genetic polymorphisms affect the human requirement for the nutrient choline. *FASEB J* 2006;20(9):1336-44.
- [154] Resseguie ME, da Costa KA, Galanko JA, Patel M, Davis IJ, Zeisel SH. Aberrant estrogen regulation of PEMT results in choline deficiency-associated liver dysfunction. *J Biol Chem* 2011;286(2):1649-58.
- [155] Hughes JF, Skaletsky H, Pyntikova T, Graves TA, van Daalen SK, Minx PJ, et al. Chimpanzee and human Y chromosomes are remarkably divergent in structure and gene content. *Nature* 2010;463(7280):536-9.
- [156] Hedelin M, Balter KA, Chang ET, Bellocco R, Klint A, Johansson JE, et al. Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006;66(14):1512-20.
- [157] Dias AG, Rousseau D, Duizer L, Cockburn M, Chiu W, Nielsen D, El-Sohemy A. Genetic variation in putative salt taste receptors and salt taste perception in humans. *Chem Senses* 2013 [Epub ahead of print] doi:10.1093/chemse/bjs090.

BÖLÜM 4

Besin Öğeleri Genetikten Nasıl Etkilenir?

TERİMLER

- Alloenzim: Varyant alele karşılık gelen amino asit dizisi değiştirilmiş enzim.
- Ekspresivite: Belirli bir genotip ile ilişkili semptom ve sağlık sonuçlarının aralığı.
- Haployetersizlik: Normalde mevcut olan iki gen kopyasından birinin kaybı.
- Homolog: Farklı bir türdeki gene fonksiyonel ve yapısal olarak benzeyen gen.
- Doğuştan metabolizma hatası: Bir metabolitin ağır olarak defektif işlenmesine atfedilmektedir.
- Penetrans: Belirli bir genotipi taşıyan ve beklenen sağlık sonucunu gösteren kişilerin yüzdesi.

ÖZET

Nutrigenetik, tüm uygulama amaçları için, spesifik beslenme faktörlerine olan doğuştan duyarlılık bilimidir. Bu bölüm, besin ögesi ve diğer besin bileşenlerinin etkilerini değiştiren genetik varyantların örneklerini vurgulayacaktır. Kitabın sınırlı alanı ve okuyucunun uygun zamanı içinde, bildirilen tüm etkileşimlerin kapsamlı bir listesini sağlamak ne bir amaç olmuştur ne de mümkündür. Bu etkileşimlerden çok fazla bulunmaktadır ve liste her gün büyümektedir. Bunun yerine, genetik bir varyantı taşıyan kişilerin besin öğelerine ve besinlere, varyantı taşımayan kişilerin verdiği yanıtta farklı olarak, nasıl özel olarak yanıt verdiğini açıklayan seçilmiş yolların ve mekanizmaların incelenmesi olacaktır. Basit bir temel kuralı hatırlamak isteyebilirsiniz: eğer bir varyant nadirse, bir şeyler muhtemelen ters gitmiştir ve varyant daha geniş çaplı yayılmamıştır. Eğer bir varyant yaygınrsa, bir şeyler doğru gitmiştir ve bir çeşit avantaj varyantın yayılmasına yardımcı olmuştur. Bahsedilen besin öğelerine verilen genotipe özgü yanıtların bazılarının sadece bir çalışmada gözlemlendiğini ve daha fazla araştırmaya ihtiyaç duyulduğunu bilmek önemlidir.

KAYNAKLAR

- [1] Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. 1902 [classical article]. *Yale J Biol Med* 2002;75(4):221-31.
- [2] Garrod Archibald. Inborn Errors of Metabolism. The Croonian Lectures delivered before the Royal College of Physicians of London, in June. *Lancet* 1908;172(4427):3.
- [3] Laxon S, Ranganath L, Timmis O. Living with alkaptonuria. *BMJ* 2011;343:d5155.
- [4] Mayatepek E, Kallas K, Anninos A, Muller E. Effects of ascorbic acid and low-protein diet in alkaptonuria. *Eur J Pediatr* 1998;157(10):867-8.
- [5] de Haas V, Carbasius Weber EC, de Klerk JB, Bakker HD, Smit GP, Huijbers WA, et al. The success of dietary protein restriction in alkaptonuria patients is age-dependent. *J Inherit Metab Dis* 1998;21(8):791-8.
- [6] Fernandez-Canon JM, Granadino B, Beltran-Valero de Bernabe D, Renedo M, Fernandez-Ruiz E, Penalva MA, et al. The molecular basis of alkaptonuria. *Nat Genet* 1996;14(1):19-24.
- [7] Howell RR. We need expanded newborn screening. *Pediatrics* 2006;117(5):1800-5.
- [8] Prado-Lima PS, Cruz IB, Schwanke CH, Netto CA, Licinio J. Human food preferences are associated with a 5-HT(2A) serotonergic receptor polymorphism. *Mol Psychiatry* 2006;11(10):889-91.
- [9] Nakamura Y, Ito Y, Aleksic B, Kushima I, Yasui-Furukori N, Inada T, et al. Influence of HTR2A polymorphisms and parental rearing on personality traits in healthy Japanese subjects. *Journal of Human Genetics* 2010;55(12):838-41.
- [10] White MJ, Young RM, Morris CP, Lawford BR. Cigarette smoking in young adults: the influence of the HTR2A T102C polymorphism and punishment sensitivity. *Drug and Alcohol Dependence* 2011;114(2e3):140-6.
- [11] Cavicchi C, Malvagia S, la Marca G, Gasperini S, Donati MA, Zammarchi E, et al. Hypocitrullinemia in expanded newborn screening by LC-MS/MS is not a reliable marker for ornithine transcarbamylase deficiency. *J Pharm Biomed Anal* 2009;49(5):1292-5.
- [12] Sathe MN, Patel AS. Update in pediatrics: focus on fat-soluble vitamins. *Nutr Clin Pract* 2010;25(4):340-6.
- [13] Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. *Horm Behav* 2011;59(3):290-5.
- [14] Ivanov PL, Wadhams MJ, Roby RK, Holland MM, Weedn VW, Parsons TJ. Mitochondrial DNA sequence heteroplasmy in the Grand Duke of Russia Georgij Romanov establishes the authenticity of the remains of Tsar Nicholas II. *Nat Genet* 1996;12(4):417-20.
- [15] Grunewald S, Fairbanks L, Genet S, Cranston T, Husing J, Leonard JV, et al. How reliable is the allopurinol load in detecting carriers for ornithine transcarbamylase deficiency? *J Inherit Metab Dis* 2004;27(2):179-86.
- [16] Yazbek SN, Spiezio SH, Nadeau JH, Buchner DA. Ancestral paternal genotype controls body weight and food intake for multiple generations. *Hum Mol Genet* 2010;19(21):4134-44.
- [17] Irwin JA, Saunier JL, Niederstatter H, Strouss KM, Sturk KA, Diegoli TM, et al. Investigation of heteroplasmy in the human mitochondrial DNA control region: a synthesis of observations from more than 5000 global population samples. *J Mol Evol* 2009;68(5):516-27.
- [18] Gibson NR, Jahoor F, Ware L, Jackson AA. Endogenous glycine and tyrosine production is maintained in adults consuming a marginal-protein diet. *Am J Clin Nutr* 2002;75(3):511-18.
- [19] Mitchell JJ, Trakadis YJ, Scriver CR. Phenylalanine hydroxylase deficiency. *Genet Med* 2011;13(8):697-707.
- [20] Hanley WB. Non-PKU mild hyperphenylalaninemia (MHP) the dilemma. *Mol Genet Metab* 2011;104(1e2):23-6.
- [21] Humphrey M, Nation J, Francis I, Boneh A. Effect of tetrahydrobiopterin on Phe/Tyr ratios and variation in Phe levels in tetrahydrobiopterin responsive PKU patients. *Mol Genet Metab* 2011;104(1e2):89-92.
- [22] Staudigl M, Gersting SW, Danecka MK, Messing DD, Woidy M, Pinkas D, et al. The interplay between genotype, metabolic state and cofactor treatment governs phenylalanine hydroxylase

- function and drug response. *Hum Mol Genet* 2011;20(13):2628-41.
- [23] Waisbren SE, Noel K, Fahrback K, Cella C, Frame D, Dorenbaum A, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Mol Genet Metab* 2007;92(1e2):63-70.
- [24] Prick BW, Hop WC, Duvekot JJ. Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: pregnancy complications and neonatal sequelae in untreated and treated pregnancies. *Am J Clin Nutr* 2012;95(2):374-82.
- [25] Webster D, Wildgoose J. Tyrosine supplementation for phenylketonuria. *Cochrane Database Syst Rev* 2010;(8):CD001507.
- [26] Kalkanoglu HS, Ahring KK, Sertkaya D, Moller LB, Romstad A, Mikkelsen I, et al. Behavioural effects of phenylalanine-free amino acid tablet supplementation in intellectually disabled adults with untreated phenylketonuria. *Acta Paediatr* 2005;94(9):1218-22.
- [27] Broer S. The role of the neutral amino acid transporter B0AT1 (SLC6A19) in Hartnup disorder and protein nutrition. *IUBMB life* 2009;61(6):591-9.
- [28] Edelmann L, Wasserstein MP, Kornreich R, Sansaricq C, Snyderman SE, Diaz GA. Maple syrup urine disease: identification and carrier-frequency determination of a novel founder mutation in the Ashkenazi Jewish population. *Am J Hum Genet* 2001;69(4):863-8.
- [29] Puckett RL, Lorey F, Rinaldo P, Lipson MH, Matern D, Sowa ME, et al. Maple syrup urine disease: further evidence that newborn screening may fail to identify variant forms. *Mol Genet Metab* 2010;100(2):136-42.
- [30] Bouchard-Mercier A, Paradis AM, Perusse L, Vohl MC. Associations between polymorphisms in genes involved in fatty acid metabolism and dietary fat intakes. *Journal of Nutrigenetics and Nutrigenomics* 2012;5(1):1-12.
- [31] Keller KL, Liang LC, Sakimura J, May D, van Belle C, Breen C, et al. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. *Obesity (Silver Spring)* 2012 May;20(5):1066-73.
- [32] Ichimura A, Hirasawa A, Poulain-Godefroy O, Bonnefond A, Hara T, Yengo L, et al. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. *Nature* 2012;483(7389):350-4.
- [33] Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 2010;142(5):687-98.
- [34] Goossens GH, Petersen L, Blaak EE, Hul G, Arner P, Astrup A, et al. Several obesity- and nutrient-related gene polymorphisms but not FTO and UCP variants modulate postabsorptive resting energy expenditure and fat-induced thermogenesis in obese individuals: the NUGENOB study. *Int J Obes (Lond)* 2009;33(6):669-79.
- [35] Uibo R, Lernmark A. GAD65 autoimmunity-clinical studies. *Advances in Immunology* 2008;100:39-78.
- [36] Suhre K, Shin SY, Petersen AK, Mohnhey RP, Meredith D, Wagele B, et al. Human metabolic individuality in biomedical and pharmaceutical research. *Nature* 2011;477(7362):54-60.
- [37] Matsuzaka T, Shimano H. Elovl6: a new player in fatty acid metabolism and insulin sensitivity. *J Mol Med (Berl)* 2009;87(4):379-84.
- [38] Morcillo S, Martin-Nunez GM, Rojo-Martinez G, Almaraz MC, Garcia-Escobar E, Mansego ML, et al. ELOVL6 genetic variation is related to insulin sensitivity: a new candidate gene in energy metabolism. *PLoS One* 2011;6(6):21198.
- [39] Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, Tucker K, et al. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. *Arch Intern Med* 2009;169(20):1897-906.
- [40] Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, Tsai MY, et al. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am J Clin Nutr* 2009;90(6):1466-75.
- [41] Tein I, Elpeleg O, Ben-Zeev B, Korman SH, Lossos A, Lev D, et al. Short-chain acyl-CoA dehydrogenase gene mutation (c.319C>T) presents with clinical heterogeneity and is candidate founder

- mutation in individuals of Ashkenazi Jewish origin. *Mol Genet Metab* 2008;93(2):179-89.
- [42] van Maldegem BT, Duran M, Wanders RJ, Waterham HR, Wijburg FA. Flavin adenine dinucleotide status and the effects of high-dose riboflavin treatment in short-chain acyl-CoA dehydrogenase deficiency. *Pediatric Research* 2010;67(3):304-8.
- [43] Nakamura MT, Nara TY. Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. *Annu Rev Nutr* 2004;24:345-76.
- [44] Ameur A, Enroth S, Johansson A, Zaboli G, Igl W, Johansson AC, et al. Genetic adaptation of fatty-acid metabolism: a human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids. *Am J Hum Genet* 2012;90(5):809-20.
- [45] Gregory MK, Gibson RA, Cook-Johnson RJ, Cleland LG, James MJ. Elongase reactions as control points in long-chain polyunsaturated fatty acid synthesis. *PLoS One* 2011;6(12):29662.
- [46] Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, et al. 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(1):38-46.
- [47] Van Duyn MA, Moser AE, Brown 3rd FR, Sacktor N, Liu A, Moser HW. The design of a diet restricted in saturated very long-chain fatty acids: therapeutic application in adrenoleukodystrophy. *Am J Clin Nutr* 1984;40(2):277-84.
- [48] Deon M, Garcia MP, Sitta A, Barschak AG, Coelho DM, Schimit GO, et al. Hexacosanoic and docosanoic acids plasma levels in patients with cerebral childhood and asymptomatic X-linked adrenoleukodystrophy: Lorenzo's oil effect. *Metabolic Brain Disease* 2008;23(1):43-9.
- [49] Hargrove JL, Greenspan P, Hartle DK. Nutritional significance and metabolism of very long chain fatty alcohols and acids from dietary waxes. *Exp Biol Med (Maywood)* 2004;229(3):215-26.
- [50] Terre'Blanche G, van der Walt MM, Bergh JJ, Mienie LJ. Treatment of an adrenomyeloneuropathy patient with Lorenzo's oil and supplementation with docosahexaenoic acid: a case report. *Lipids Health Dis* 2011;10:152.
- [51] Cappa M, Bizzarri C, Petroni A, Carta G, Cordeddu L, Valeriani M, et al. A mixture of oleic, erucic and conjugated linoleic acids modulates cerebrospinal fluid inflammatory markers and improve somatosensorial evoked potential in X-linked adrenoleukodystrophy female carriers. *J Inher Metab Dis* 2012;35(5):899-907.
- [52] Lemaitre RN, Tanaka T, Tang W, Manichaikul A, Foy M, Kabagambe EK, et al. Genetic loci associated with plasma phospholipid n-3 fatty acids: a meta-analysis of genome-wide association studies from the CHARGE Consortium. *PLoS Genet* 2011;7(7):1002193.
- [53] Merino DM, Johnston H, Clarke S, Roke K, Nielsen D, Badawi A, et al. Polymorphisms in FADS1 and FADS2 alter desaturase activity in young Caucasian and Asian adults. *Mol Genet Metab* 2011;103(2):171-8.
- [54] Dumont J, Huybrechts I, Spinneker A, Gottrand F, Grammatikaki E, Bevilacqua N, et al. FADS1 genetic variability interacts with dietary alpha-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. *J Nutr* 2011;141(7):1247-53.
- [55] Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med* 2004;350(1):29-37.
- [56] Kohlschütter A, Santer R, Lukacs Z, Altenburg C, Kemper MJ, Ruther K. A child with night blindness: Preventing serious symptoms of refsum disease. *Journal of Child Neurology* 2012 May;27(5):654-6.
- [57] Yang C, Yu L, Li W, Xu F, Cohen JC, Hobbs HH. Disruption of cholesterol homeostasis by plant sterols. *J Clin Invest* 2004;114(6):813-22.
- [58] Yamanashi Y, Takada T, Suzuki H. Niemann-Pick C1-like 1 overexpression facilitates ezetimibe-sensitive cholesterol and beta-sitosterol uptake in CaCo-2 cells. *J Pharmacol Exp Ther* 2007;320(2):559-64.
- [59] Rios J, Stein E, Shendure J, Hobbs HH, Cohen JC. Identification by whole-genome resequencing of gene defect responsible for severe hypercholesterolemia. *Hum Mol Genet* 2010;19(22):4313-18.
- [60] Herron KL, Vega-Lopez S, Conde K, Ramjiganesh T, Shachter NS, Fernandez ML. Men classified as hypo- or hyperresponders to dietary cholesterol feeding exhibit differences in lipoprotein me-

- tabolism. *J Nutr* 2003;133(4):1036-42.
- [61] Chakrabarty G, Manjunatha S, Bijlani RL, Ray RB, Mahapatra SC, Mehta N, et al. The effect of ingestion of egg on the serum lipid profile of healthy young Indians. *Indian J Physiol Pharmacol* 2004;48(3):286-92.
- [62] Wolff E, Vergnes MF, Defoort C, Planells R, Portugal H, Nicolay A, et al. Cholesterol absorption status and fasting plasma cholesterol are modulated by the microsomal triacylglycerol transfer protein -493 G/T polymorphism and the usual diet in women. *Genes Nutr* 2011;6(1):71-9.
- [63] Masson LF, McNeill G, Avenell A. Genetic variation and the lipid response to dietary intervention: a systematic review. *Am J Clin Nutr* 2003;77(5):1098-111.
- [64] Sarkkinen E, Korhonen M, Erkkilä A, Ebeling T, Uusitupa M. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *Am J Clin Nutr* 1998;68(6):1215-22.
- [65] Herron KL, McGrane MM, Waters D, Lofgren IE, Clark RM, Ordovas JM, et al. The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. *J Nutr* 2006;136(5):1161-5.
- [66] Clark RM, Herron KL, Waters D, Fernandez ML. Hypo- and hyperresponse to egg cholesterol predicts plasma lutein and beta-carotene concentrations in men and women. *J Nutr* 2006;136(3):601-7.
- [67] Lebenthal E, Khin Maung U, Zheng BY, Lu RB, Lerner A. Small intestinal glucoamylase deficiency and starch malabsorption: a newly recognized alpha-glucosidase deficiency in children. *J Pediatr* 1994;124(4):541-6.
- [68] Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. *BMC Evol Biol* 2010;10:36.
- [69] Peterson ML, Herber R. Intestinal sucrase deficiency. *Trans Assoc Am Physicians* 1967;80:275-83.
- [70] Arola H, Koivula T, Karvonen AL, Jokela H, Ahola T, Isokoski M. Low trehalase activity is associated with abdominal symptoms caused by edible mushrooms. *Scand J Gastroenterol* 1999;34(9):898-903.
- [71] Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, et al. Detection of large-scale variation in the human genome. *Nat Genet* 2004;36(9):949-51.
- [72] Acosta PB, Gross KC. Hidden sources of galactose in the environment. *Eur J Pediatr* 1995;154(7 Suppl. 2):S87-92.
- [73] Brivet M, Raymond JP, Konopka P, Odievre M, Lemonnier A. Effect of lactation in a mother with galactosemia. *J Pediatr* 1989;115(2):280-2.
- [74] Kuokkanen M, Kokkonen J, Enattah NS, Ylisaukko-Oja T, Komu H, Varilo T, et al. Mutations in the translated region of the lactase gene (LCT) underlie congenital lactase deficiency. *Am J Hum Genet* 2006;78(2):339-44.
- [75] Thain RI. Bovine infertility possibly caused by subterranean clover. Further report and herd histories. *Aust Vet J* 1966;42(6):199-203.
- [76] Kalela K, Heinonen K, Saloniemi H. Plant oestrogens; the cause of decreased fertility in cows. A case report. *Nord Vet Med* 1984;36(3e4):124-9.
- [77] Stevens JF, Page JE. Xanthohumol and related prenylflavonoids from hops and beer: to your good health! *Phytochemistry* 2004;65(10):1317-30.
- [78] Fang L, Ahn JK, Wodziak D, Sibley E. The human lactase persistence-associated SNP -13910*T enables in vivo functional persistence of lactase promoter-reporter transgene expression. *Hum Genet* 2012 Jul;131(7):1153-9.
- [79] Harris EE, Meyer D. The molecular signature of selection underlying human adaptations. *Am J Phys Anthropol* 2006;(Suppl. 43):89-130.
- [80] Lovelace HY, Barr SI. Diagnosis, symptoms, and calcium intakes of individuals with self-reported lactose intolerance. *Journal of the American College of Nutrition* 2005;24(1):51-7.
- [81] Marton A, Xue X, Szilagyí A. Meta-analysis: the diagnostic accuracy of lactose breath hydrogen or lactose tolerance tests for predicting the North European lactase polymorphism C/T-13910. *Aliment Pharmacol Ther* 2012;35(4):429-40.

- [82] Matthews SB, Waud JP, Roberts AG, Campbell AK. Systemic lactose intolerance: a new perspective on an old problem. *Postgrad Med J* 2005;81(953):167-73.
- [83] VonkRJ, Stellaard F, Priebe MG, Koetse HA, Hagedoorn RE, DeBruijn S, et al. The 13C/2H-glucose test for determination of small intestinal lactase activity. *Eur J Clin Invest* 2001;31(3):226-33.
- [84] Dahlqvist A. Assay of intestinal disaccharidases. *Scand J Clin Lab Invest* 1984;44(2):169-72.
- [85] Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995;333(1):1-4.
- [86] Vernia P, Di Camillo M, Marinaro V. Lactose malabsorption, irritable bowel syndrome and self-reported milk intolerance. *Digestive and Liver Disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2001;33(3):234-9.
- [87] Obermayer-Pietsch BM, Bonelli CM, Walter DE, Kuhn RJ, Fahrleitner-Pammer A, Berghold A, et al. Genetic predisposition for adult lactose intolerance and relation to diet, bone density, and bone fractures. *Journal of Bone and Mineral Research: the official journal of the American Society for Bone and Mineral Research* 2004;19(1):42-7.
- [88] Honkanen R, Kroger H, Alhava E, Turpeinen P, Tuppurainen M, Saarikoski S. Lactose intolerance associated with fractures of weight-bearing bones in Finnish women aged 38e57 years. *Bone* 1997;21(6):473-7.
- [89] Martin MG, Turk E, Lostao MP, Kerner C, Wright EM. Defects in Na⁺/glucose cotransporter (SGLT1) trafficking and function cause glucose-galactose malabsorption. *Nat Genet* 1996;12(2):216-20.
- [90] Martin MG, Turk E, Kerner C, Zabel B, Wirth S, Wright EM. Prenatal identification of a heterozygous status in two fetuses at risk for glucose-galactose malabsorption. *Prenat Diagn* 1996;16(5):458-62.
- [91] Kriegshauser G, Halsall D, Rauscher B, Oberkanins C. Semi-automated, reverse-hybridization detection of multiple mutations causing hereditary fructose intolerance. *Mol Cell Probes* 2007;21(3):226-8.
- [92] Coffee EM, Tolan DR. Mutations in the promoter region of the aldolase B gene that cause hereditary fructose intolerance. *J Inherit Metab Dis* 2010;33(6):715-25.
- [93] Cox TM. Fructose intolerance: diet and inheritance. *Proc Nutr Soc* 1991;50(2):305-9.
- [94] Yasawy MI, Folsch UR, Schmidt WE, Schwend M. Adult hereditary fructose intolerance. *World J Gastroenterol* 2009;15(19):2412-3.
- [95] Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004;79(4):537-43.
- [96] Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent monosaccharides. *Gut* 1986;27(10):1161-8.
- [97] Beyer PL, Caviar EM, McCallum RW. Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults. *J Am Diet Assoc* 2005;105(10):1559-66.
- [98] Szilagyi A, Malolepszy P, Yesovitch S, Vinokuroff C, Nathwani U, Cohen A, et al. Fructose malabsorption may be gender dependent and fails to show compensation by colonic adaptation. *Dig Dis Sci* 2007;52(11):2999-3004.
- [99] Born P, Sekatcheva M, Rosch T, Classen M. Carbohydrate malabsorption in clinical routine: a prospective observational study. *Hepatogastroenterology* 2006;53(71):673-7.
- [100] Tsampalieros A, Beauchamp J, Boland M, Mack DR. Dietary fructose intolerance in children and adolescents. *Arch Dis Child* 2008;93(12):1078.
- [101] Reyes-Huerta JU, de la Cruz-Patino E, Ramirez-Gutierrez de Velasco A, Zamudio C, RemesTroche JM. Fructose intolerance in patients with irritable bowel syndrome: a case-control study. *Rev Gastroenterol Mex* 2010;75(4):405-11.
- [102] Choi YK, Kraft N, Zimmerman B, Jackson M, Rao SS. Fructose intolerance in IBS and utility of fructose-restricted diet. *J Clin Gastroenterol* 2008;42(3):233-8.
- [103] Skoog SM, Bharucha AE, Zinsmeister AR. Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterol Motil* 2008;20(5):505-11.

- [104] Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005;81(2):341-54.
- [105] Asp NG, Berg NO, Dahlqvist A, Gudmand-Hoyer E, Jarnum S, McNair A. Intestinal disaccharidases in Greenland Eskimos. *Scand J Gastroenterol* 1975;10(5):513-19.
- [106] Robayo-Torres CC, Opekun AR, Quezada-Calvillo R, Villa X, Smith EO, Navarrete M, et al. 13C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr* 2009;48(4):412-18.
- [107] Mones RL, Yankah A, Duelfer D, Bustami R, Mercer G. Disaccharidase deficiency in pediatric patients with celiac disease and intact villi. *Scand J Gastroenterol* 2011;46(12):1429-34.
- [108] Treem WR. Congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1995;21(1):1-14.
- [109] Minai-Tehrani D, Ghaffari M, Sobhani-Damavandifar Z, Minoui S, Alavi S, Osmani R, et al. Ranitidine induces inhibition and structural changes in sucrase. *J Enzyme Inhib Med Chem* 2011 Aug 18 [Epub ahead of print].
- [110] van Can JG, Ijzerman TH, van Loon LJ, Brouns F, Blaak EE. Reduced glycaemic and insulin-aemic responses following trehalose ingestion: implications for postprandial substrate use. *Br J Nutr* 2009;102(10):1395-9.
- [111] Gudmand-Hoyer E, Fenger HJ, Skovbjerg H, Kern-Hansen P, Madsen PR. Trehalase deficiency in Greenland. *Scand J Gastroenterol* 1988;23(7):775-8.
- [112] Oku T, Nakamura S. Estimation of intestinal trehalase activity from a laxative threshold of trehalose and lactulose on healthy female subjects. *Eur J Clin Nutr* 2000;54(10):783-8.
- [113] Bergoz R, Vallotton MC, Loizeau E. Trehalase deficiency. Prevalence and relation to single-cell protein food. *Ann Nutr Metab* 1982;26(5):291-5.
- [114] Buts JP, Stilmant C, Bernasconi P, Neirincq C, De Keyser N. Characterization of alpha, alphan-trehalase released in the intestinal lumen by the probiotic *Saccharomyces boulardii*. *Scand J Gastroenterol* 2008;43(12):1489-96.
- [115] Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, et al. Glucose-6-phosphatase deficiency. *Orphanet J Rare Dis* 2011;6:27.
- [116] Nuoffer JM, Mullis PE, Wiesmann UN. Treatment with low-dose diazoxide in two growthretarded prepubertal girls with glycogen storage disease type Ia resulted in catch-up growth. *J Inher Metab Dis* 1997;20(6):790-8.
- [117] Zimatkin SM, Liopo AV, Deitrich RA. Distribution and kinetics of ethanol metabolism in rat brain. *Alcohol Clin Exp Res* 1998;22(8):1623-7.
- [118] Quertemont E. Genetic polymorphism in ethanol metabolism: acetaldehyde contribution to alcohol abuse and alcoholism. *Mol Psychiatry* 2004;9(6):570-81.
- [119] Thomasson HR, Beard JD, Li TK. ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. *Alcohol Clin Exp Res* 1995;19(6):1494-9.
- [120] Ji YB, Tae K, Ahn TH, Lee SH, Kim KR, Park CW, et al. ADH1B and ALDH2 polymorphisms and their associations with increased risk of squamous cell carcinoma of the head and neck in the Korean population. *Oral Oncol* 2011;47(7):583-7.
- [121] Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer* 2007;7(8):599-612.
- [122] Gizer IR, Edenberg HJ, Gilder DA, Wilhelmsen KC, Ehlers CL. Association of alcohol dehydrogenase genes with alcohol-related phenotypes in a native american community sample. *Alcohol Clin Exp Res* 2011;35(11):2008-18.
- [123] Pochareddy S, Edenberg HJ. Variation in the ADH1B proximal promoter affects expression. *Chem Biol Interact* 2011;191(1e3):38-41.
- [124] Preuss UW, Ridinger M, Rujescu D, Samochowiec J, Fehr C, Wurst FM, et al. Association of ADH4 genetic variants with alcohol dependence risk and related phenotypes: results from a larger multicenter association study. *Addict Biol* 2011;16(2):323-33.
- [125] Higuchi S, Matsushita S, Muramatsu T, Murayama M, Hayashida M. Alcohol and aldehyde dehydrogenase genotypes and drinking behavior in Japanese. *Alcohol Clin Exp Res* 1996;20(3):493-7.

- [126] Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Dietary Sodium Reduction Time for Choice. *MMWR Morb Mort Weekly Rep* 2012;61:89-91.
- [127] GenSalt Collaborative Research Group. GenSalt: rationale, design, methods and baseline characteristics of study participants. *J Human Hypertension* 2007;21(8):639-46.
- [128] Hannila-Handelberg T, Kontula K, Tikkanen I, Tikkanen T, Fyhrquist F, Helin K, et al. Common variants of the beta and gamma subunits of the epithelial sodium channel and their relation to plasma renin and aldosterone levels in essential hypertension. *BMC Med Genet* 2005;6:4.
- [129] Zhao Q, Gu D, Hixson JE, Liu DP, Rao DC, Jaquish CE, et al. Common variants in epithelial sodium channel genes contribute to salt sensitivity of blood pressure: The GenSalt study. *Circ Cardiovasc Genet* 2011;4(4):375-80.
- [130] Su YR, Rutkowski MP, Klanke CA, Wu X, Cui Y, Pun RY, et al. A novel variant of the beta-subunit of the amiloride-sensitive sodium channel in African Americans. *J Am Soc Nephrol* 1996;7(12):2543-9.
- [131] Dong YB, Zhu HD, Baker EH, Sagnella GA, MacGregor GA, Carter ND, et al. T594M and G442V polymorphisms of the sodium channel beta subunit and hypertension in a black population. *J Human Hypertension* 2001;15(6):425-30.
- [132] Miettinen HE, Piippo K, Hannila-Handelberg T, Paukku K, Hiltunen TP, Gautschi I, et al. Lico-rice-induced hypertension and common variants of genes regulating renal sodium reabsorption. *Annals Med* 2010;42(6):465-74.
- [133] Lanzani C, Citterio L, Jankaricova M, Sciarone MT, Barlassina C, Fattori S, et al. Role of the adducin family genes in human essential hypertension. *J Hypertens* 2005;23(3):543-9.
- [134] Watkins WS, Rohrwasser A, Peiffer A, Leppert MF, Lalouel JM, Jorde LB. AGT genetic variation, plasma AGT, and blood pressure: An analysis of the Utah Genetic Reference Project pedigrees. *Am J Hypertension* 2010;23(8):917-23
- [135] Beeks E, Kessels AG, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: a systematic review. *J Hypertens* 2004;22(7):1243-9.
- [136] Ni S, Zhang Y, Deng Y, Gong Y, Huang J, Bai Y, et al. AGT M235T polymorphism contributes to risk of preeclampsia: evidence from a meta-analysis. *Journal of the renin-angiotensinaldosterone system: JRAAS* 2012;13(3):379-86.
- [137] Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de La Sierra A. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001;38(5):1204-9.
- [138] Wang Y, Li B, Zhao W, Liu P, Zhao Q, Chen S, et al. Association study of G protein-coupled receptor kinase 4 gene variants with essential hypertension in northern Han Chinese. *Ann Human Genet* 2006;70(Pt 6):778-83.
- [139] Sanada H, Yatabe J, Midorikawa S, Hashimoto S, Watanabe T, Moore JH, et al. Singlenucleotide polymorphisms for diagnosis of salt-sensitive hypertension. *Clin Chem* 2006;52(3):352-60.
- [140] Caprioli J, Mele C, Mossali C, Gallizioli L, Giacchetti G, Noris M, et al. Polymorphisms of EDN-RB, ATG, and ACE genes in salt-sensitive hypertension. *Can J Physiol Pharmacol* 2008;86(8):505-10.
- [141] Dos Santos EA, Dahly-Vernon AJ, Hoagland KM, Roman RJ. Inhibition of the formation of EETs and 20-HETE with 1-aminobenzotriazole attenuates pressure natriuresis. *Am J Physiol Reg Int Comp Physiol* 2004;287(1):R58-68.
- [142] Williams JS, Hopkins PN, Jeunemaitre X, Brown NJ. CYP4A11 T8590C polymorphism, salt-sensitive hypertension, and renal blood flow. *J Hypertens* 2011;29(10):1913-8.
- [143] Ledford H. Africa yields two full human genomes. *Nature* 2010;463(7283):857.
- [144] Lee BH, Cho HY, Lee H, Han KH, Kang HG, Ha IS, et al. Genetic basis of Bartter syndrome in Korea. *Nephrol Dial Transplant* 2012;27(4):1516-21.
- [145] Sile S, Velez DR, Gillani NB, Narsia T, Moore JH, George Jr AL, et al. CLCNKB-T481S and essential hypertension in a Ghanaian population. *J Hypertens* 2009;27(2):298-304.
- [146] Kelly TN, Hixson JE, Rao DC, Mei H, Rice TK, Jaquish CE, et al. Genome-wide linkage and positional candidate gene study of blood pressure response to dietary potassium intervention: the

- genetic epidemiology network of salt sensitivity study. *Circ Cardiovasc Genet* 2010;3(6):539-47.
- [147] He Y, Han L, Li W, Shu X, Zhao C, Bi M, et al. Effects of the calcium-sensing receptor A986S polymorphism on serum calcium and parathyroid hormone levels in healthy individuals: a meta-analysis. *Gene* 2012;491(2):110-15.
- [148] Shakhssalim N, Kazemi B, Basiri A, Houshmand M, Pakmanesh H, Golestan B, et al. Association between calcium-sensing receptor gene polymorphisms and recurrent calcium kidney stone disease: a comprehensive gene analysis. *Scand J Urol Nephrol* 2010;44(6):406-12.
- [149] Bacsi K, Hitre E, Kosa JP, Horvath H, Lazary A, Lakatos PL, et al. Effects of the lactase 13910 C/T and calcium-sensor receptor A986S G/T gene polymorphisms on the incidence and recurrence of colorectal cancer in Hungarian population. *BMC Cancer* 2008;8:317.
- [150] Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE, et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007;86(3):743-51.
- [151] Mei Z, Cogswell ME, Looker AC, Pfeiffer CM, Cusick SE, Lacher DA, et al. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999e2006. *Am J Clin Nutr* 2011;93(6):1312-20.
- [152] Gambling L, Kennedy C, McArdle HJ. Iron and copper in fetal development. *Semin Cell Dev Biol* 2011 Aug;22(6):637-44.
- [153] Brissot P, Bardou-Jacquet E, Jouanolle AM, Loreal O. Iron disorders of genetic origin: a changing world. *Trends Mol Med* 2011 Dec;17(12):707-13.
- [154] Lucotte G, Mercier G. Celtic origin of the C282Y mutation of hemochromatosis. *Genet Test* 2000;4(2):163-9.
- [155] Mayr R, Janecke AR, Schranz M, Griffiths WJ, Vogel W, Pietrangelo A, et al. Ferroportin disease: a systematic meta-analysis of clinical and molecular findings. *J Hepatol* 2010;53(5):941-9.
- [156] Frank KM, Schneewind O, Shieh WJ. Investigation of a researcher's death due to septicemic plague. *N Engl J Med* 2011;364(26):2563-4.
- [157] Galan SR, Kann PH, Gress TM, Michl P. *Listeria monocytogenes*-induced bacterial peritonitis caused by contaminated cheese in a patient with haemochromatosis. *Zeitschrift fur Gastroenterologie* 2011;49(7):832-5.
- [158] Baker MA, Wilson D, Wallengren K, Sandgren A, Iartchouk O, Broodie N, et al. Polymorphisms in the gene that encodes the iron transport protein ferroportin 1 influence susceptibility to tuberculosis. *J Inf Dis* 2012;205(7):1043-7.
- [159] Burke W, Imperatore G, McDonnell SM, Baron RC, Khoury MJ. Contribution of different HFE genotypes to iron overload disease: a pooled analysis. *Genet Med* 2000;2(5):271-7.
- [160] Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. Total mortality by transferrin saturation levels: two general population studies and a metaanalysis. *Clin Chem* 2011;57(3):459-66.
- [161] Gerhard GS, Chokshi R, Still CD, Benotti P, Wood GC, Freedman-Weiss M, et al. The influence of iron status and genetic polymorphisms in the HFE gene on the risk for postoperative complications after bariatric surgery: a prospective cohort study in 1,064 patients. *Patient Saf Surg* 2011;5(1):1.
- [162] Aranda N, Viteri FE, Montserrat C, Arija V. Effects of C282Y, H63D, and S65C HFE gene mutations, diet, and life-style factors on iron status in a general Mediterranean population from Tarra-gona, Spain. *Ann Hematol* 2010;89(8):767-73.
- [163] Heath AL, Roe MA, Oyston SL, Gray AR, Williams SM, Fairweather-Tait SJ. Blood loss is a stronger predictor of iron status in men than C282Y heterozygosity or diet. *Journal of the American College of Nutrition* 2008;27(1):158-67.
- [164] McLaren CE, Garner CP, Constantine CC, McLachlan S, Vulpe CD, Snively BM, et al. Genome-wide association study identifies genetic loci associated with iron deficiency. *PLoS One* 2011;6(3):17390.
- [165] Tanaka T, Roy CN, Yao W, Matteini A, Semba RD, Arking D, et al. A genome-wide association analysis of serum iron concentrations. *Blood* 2010;115(1):94-6.
- [166] Grasberger H, Refetoff S. Genetic causes of congenital hypothyroidism due to dysmorphogene-

sis. *Curr Opin Pediatr* 2011 Aug;23(4):421-8.

- [167] Bo'ttcher Y, Eszlinger M, To'njes A, Paschke R. The genetics of euthyroid familial goiter. *Trends Endocrinol Metab* 2005;16(7):314-9.
- [168] Singer J, Eszlinger M, Wicht J, Paschke R. Evidence for a more pronounced effect of genetic predisposition than environmental factors on goitrogenesis by a case control study in an area with low normal iodine supply. *Horm Metab Res* 2011;43(5):349-54.
- [169] Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP. The Pendred syndrome gene encodes a chloride-iodide transport protein. *Nat Genet* 1999;21(4):440-3.
- [170] King JC. Zinc: an essential but elusive nutrient. *Am J Clin Nutr* 2011;94(2):679S-84S.
- [171] John LB, Ward AC. The Ikaros gene family: transcriptional regulators of hematopoiesis and immunity. *Molecular Immunology* 2011;48(9e10):1272-8.
- [172] Schmitt S, Kury S, Giraud M, Dreno B, Kharfi M, Bezieau S. An update on mutations of the SLC39A4 gene in acrodermatitis enteropathica. *Hum Mutat* 2009;30(6):926-33.
- [173] Kharfi M, El Fekih N, Aounallah-Skhiri H, Schmitt S, Fazaa B, Kury S, et al. Acrodermatitis enteropathica: a review of 29 Tunisian cases. *Int J Dermatol* 2010;49(9):1038-44.
- [174] Klevay LM. Lack of a recommended dietary allowance for copper may be hazardous to your health. *Journal of the American College of Nutrition* 1998;17(4):322-6.
- [175] Chowanadisai W, Lonnerdal B, Kelleher SL. Identification of a mutation in SLC30A2 (ZnT-2) in women with low milk zinc concentration that results in transient neonatal zinc deficiency. *J Biol Chem* 2006;281(51):39699-707.
- [176] Nicolson TJ, Bellomo EA, Wijesekara N, Loder MK, Baldwin JM, Gyulkhandanyan AV, et al. Insulin storage and glucose homeostasis in mice null for the granule zinc transporter ZnT8 and studies of the type 2 diabetes-associated variants. *Diabetes* 2009;58(9):2070-83.
- [177] Kawasaki E. ZnT8 and type 1 diabetes [Review]. *Endocrine J* 2012;59(7):531-7.
- [178] Kanoni S, Nettleton JA, Hivert MF, Ye Z, van Rooij FJ, Shungin D, et al. Total zinc intake may modify the glucose-raising effect of a zinc transporter (SLC30A8) variant: a 14-cohort metaanalysis. *Diabetes* 2011;60(9):2407-16.
- [179] Giacconi R, Cipriano C, Muti E, Costarelli L, Maurizio C, Saba V, et al. Novel -209A/G MT2A polymorphism in old patients with type 2 diabetes and atherosclerosis: relationship with inflammation (IL-6) and zinc. *Biogerontology* 2005;6(6):407-13.
- [180] EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012;56(3):671-85.
- [181] Barik A, Mishra B, Shen L, Mohan H, Kadam RM, Dutta S, et al. Evaluation of a new copper(II)-curcumin complex as superoxide dismutase mimic and its free radical reactions. *Free Radic Biol Med* 2005;39(6):811-22.
- [182] Gromadzka G, Chabik G, Mendel T, Wierzchowska A, Rudnicka M, Czlonkowska A. Middle-aged heterozygous carriers of Wilson's disease do not present with significant phenotypic deviations related to copper metabolism. *Journal of Genetics* 2010;89(4):463-7.
- [183] Fuchs SA, Harakalova M, van Haften G, van Hasselt PM, Cuppen E, Houwen RH. Application of exome sequencing in the search for genetic causes of rare disorders of copper metabolism. *Metallomics: Integ Biometal Sci* 2012 Jul 28;4(7):606-13.
- [184] Combs Jr GE, Watts JC, Jackson MI, Johnson LK, Zeng H, Scheett AJ, et al. Determinants of selenium status in healthy adults. *Nutrition J* 2011;10:75.
- [185] Cominetti C, de Bortoli MC, Purgatto E, Ong TP, Moreno FS, Garrido Jr AB, et al. Associations between glutathione peroxidase-1 Pr0198Leu polymorphism, selenium status, and DNA damage levels in obese women after consumption of Brazil nuts. *Nutrition* 2011;27(9):891-6.
- [186] Chen J, Cao Q, Qin C, Shao P, Wu Y, Wang M, et al. GPx-1 polymorphism (rs1050450) contributes to tumor susceptibility: evidence from meta-analysis. *J Canc Res Clin Oncol* 2011;137(10):1553-61.
- [187] Xiong YM, Mo XY, Zou XZ, Song RX, Sun WY, Lu W, et al. Association study between polymorphisms in selenoprotein genes and susceptibility to Kashin-Beck disease. *Osteoarthritis and cartilage/OARS. Osteoarthritis Research Society* 2010;18(6):817-24.
- [188] Reiss J, Hahnwald R. Molybdenum cofactor deficiency: Mutations in GPHN, MOCS1, and

- MOCS2. *Hum Mutat* 2011;32(1):10-8.
- [189] Veldman A, Santamaria-Araujo JA, Sollazzo S, Pitt J, Gianello R, Yaplıto-Lee J, et al. Successful treatment of molybdenum cofactor deficiency type A with cPMP. *Pediatrics* 2010;125(5):e1249-54.
- [190] Johnson JL, Coyne KE, Rajagopalan KV, Van Hove JL, Mackay M, Pitt J, et al. Molybdopterin synthase mutations in a mild case of molybdenum cofactor deficiency. *Am J Med Genet* 2001;104(2):169-73.
- [191] Touati G, Rusthoven E, Depondt E, Dorche C, Duran M, Heron B, et al. Dietary therapy in two patients with a mild form of sulphite oxidase deficiency. Evidence for clinical and biological improvement. *J Inher Metab Dis* 2000;23(1):45-53.
- [192] Eck P, Erichsen HC, Taylor JG, Yeager M, Hughes AL, Levine M, et al. Comparison of the genomic structure and variation in the two human sodium-dependent vitamin C transporters, SLC23A1 and SLC23A2. *Hum Genet* 2004;115(4):285-94.
- [193] Savini I, Rossi A, Pierro C, Avigliano L, Catani MV. SVCT1 and SVCT2: key proteins for vitamin C uptake. *Amino Acids* 2008;34(3):347-55.
- [194] Corpe CP, Tu H, Eck P, Wang J, Faulhaber-Walter R, Schnermann J, et al. Vitamin C transporter Slc23a1 links renal reabsorption, vitamin C tissue accumulation, and perinatal survival in mice. *J Clin Invest* 2010;120(4):1069-83.
- [195] Erichsen HC, Engel SA, Eck PK, Welch R, Yeager M, Levine M, et al. Genetic variation in the sodium-dependent vitamin C transporters, SLC23A1, and SLC23A2 and risk for preterm delivery. *Am J Epidemiol* 2006;163(3):245-54.
- [196] Block G, Shaikh N, Jensen CD, Volberg V, Holland N. Serum vitamin C and other biomarkers differ by genotype of phase 2 enzyme genes GSTM1 and GSTT1. *Am J Clin Nutr* 2011;94(3):929-37.
- [197] Cahill LE, Fontaine-Bisson B, El-Sohemy A. Functional genetic variants of glutathione S-transferase protect against serum ascorbic acid deficiency. *Am J Clin Nutr* 2009;90(5):1411-17.
- [198] Linster CL, Van Schaftingen E, Vitamin C. Biosynthesis, recycling and degradation in mammals. *The FEBS journal* 2007;274(1):1-22.
- [199] Delanghe JR, Langlois MR, De Buyzere ML, Na N, Ouyang J, Speeckaert MM, et al. Vitamin C deficiency: more than just a nutritional disorder. *Genes Nutr* 2011;6(4):341-6.
- [200] Savy M, Hennig BJ, Doherty CP, Fulford AJ, Bailey R, Holland MJ, et al. Haptoglobin and sickle cell polymorphisms and risk of active trachoma in Gambian children. *PLoS One* 2010;5(6):11075.
- [201] Chiossi G, Neri I, Cavazzuti M, Basso G, Facchinetti F. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. *Obstetrical & Gynecological Survey* 2006;61(4):255-68.
- [202] Luigetti M, Sabatelli M, Cianfoni A. Wernicke's encephalopathy following chronic diarrhoea. *Acta Neurologica Belgica* 2011;111(3):257.
- [203] Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007;6(5):442-55.
- [204] Blass JP, Gibson GE. Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. *N Engl J Med* 1977;297(25):1367-70.
- [205] Coy JF, Dressler D, Wilde J, Schubert P. Mutations in the transketolase-like gene TKTL1: clinical implications for neurodegenerative diseases, diabetes and cancer. *Clin Lab* 2005;51(5e6):257-73.
- [206] Kono S, Miyajima H, Yoshida K, Togawa A, Shirakawa K, Suzuki H. Mutations in a thiamine transporter gene and Wernicke's-like encephalopathy. *N Engl J Med* 2009;360(17):1792-4.
- [207] Heap LC, Pratt OE, Ward RJ, Waller S, Thomson AD, Shaw GK, et al. Individual susceptibility to Wernicke-Korsakoff syndrome and alcoholism-induced cognitive deficit: impaired thiamine utilization found in alcoholics and alcohol abusers. *Psychiatric genetics* 2002;12(4):217-24.
- [208] Guerrini I, Thomson AD, Gurling HM. Molecular genetics of alcohol-related brain damage. *Alcohol Alcohol* 2009;44(2):166-70.
- [209] Thomson AD, Marshall EJ. The natural history and pathophysiology of Wernicke's Encephalopathy and Korsakoff's Psychosis. *Alcohol Alcohol* 2006;41(2):151-8.
- [210] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the

- cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.
- [211] Dalla Barba G. Different patterns of confabulation. *Cortex* 1993;29(4):567-81.
- [212] Fregly AR, Smith MJ, Graybiel A. Revised normative standards of performance of men on a quantitative ataxia test battery. *Acta Otolaryngol* 1973;75(1):10-6.
- [213] Sullivan EV, Rohlfing T, Pfefferbaum A. Pontocerebellar volume deficits and ataxia in alcoholic men and women: no evidence for “telescoping.” *Psychopharmacology (Berl)* 2010;208(2):279-90.
- [214] Chiong MA, Sim KG, Carpenter K, Rhead W, Ho G, Olsen RK, et al. Transient multiple acylCoA dehydrogenation deficiency in a newborn female caused by maternal riboflavin deficiency. *Mol Genet Metab* 2007;92(1e2):109-14.
- [215] Ho G, Yonezawa A, Masuda S, Inui K, Sim KG, Carpenter K, et al. Maternal riboflavin deficiency, resulting in transient neonatal-onset glutaric aciduria Type 2, is caused by a microdeletion in the riboflavin transporter gene GPR172B. *Hum Mutat* 2011;32(1):E1976-84.
- [216] Bosch AM, Abeling NG, Ijlst L, Knoester H, van der Pol WL, Stroomer AE, et al. Brown-Vialetto Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. *J Inherit Metab Dis* 2011;34(1):159-64.
- [217] Oduho GW, Han Y, Baker DH. Iron deficiency reduces the efficacy of tryptophan as a niacin precursor. *J Nutr* 1994;124(3):444-50.
- [218] Consolazio CF, Johnson HL, Krzywicki HJ, Witt NF. Tryptophan-niacin interrelationships during acute fasting and caloric restriction in humans. *Am J Clin Nutr* 1972;25(6):572-5.
- [219] Horwitt MK, Harper AE, Henderson LM. Niacin-tryptophan relationships for evaluating niacin equivalents. *Am J Clin Nutr* 1981;34(3):423-7.
- [220] Fukuwatari T, Shibata K. Effect of nicotinamide administration on the tryptophan-nicotinamide pathway in humans. *Int J Vitam Nutr Res* 2007;77(4):255-62.
- [221] Pique-Duran E, Perez-Cejudo JA, Comeselle D, Palacios-Llopis S, Garcia-Vazquez O. Pellagra: a clinical, histopathological, and epidemiological study of 7 cases. *Actas Dermo-sifiliograficas* 2012;103(1):51-8.
- [222] Tanaka T, Scheet P, Giusti B, Bandinelli S, Piras MG, Usala G, et al. Genome-wide association study of vitamin B₆, vitamin B₁₂, folate, and homocysteine blood concentrations. *Am J Hum Genet* 2009;84(4):477-82.
- [223] Hazra A, Kraft P, Lazarus R, Chen C, Chanock SJ, Jacques P, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. *Hum Mol Genet* 2009;18(23):4677-87.
- [224] Afman LA, Trijbels FJ, Blom HJ. The H475Y polymorphism in the glutamate carboxypeptidase II gene increases plasma folate without affecting the risk for neural tube defects in humans. *J Nutr* 2003;133(1):75-7.
- [225] Ashfield-Watt PA, Pullin CH, Whiting JM, Clark ZE, Moat SJ, Newcombe RG, et al. Methylene tetrahydrofolate reductase 677C>T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: a randomized controlled trial. *Am J Clin Nutr* 2002;76(1):180-6.
- [226] Yazdanpanah N, Uitterlinden AG, Zillikens MC, Jhamai M, Rivadeneira F, Hofman A, et al. Low dietary riboflavin but not folate predicts increased fracture risk in postmenopausal women homozygous for the MTHFR 677 T allele. *Journal of Bone and Mineral Research: the official journal of the American Society for Bone and Mineral Research* 2008;23(1):86-94.
- [227] Wilson CP, Ward M, McNulty H, Strain JJ, Trouton TG, Horigan G, et al. Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow-up. *Am J Clin Nutr* 2012;95(3):766-72.
- [228] McNulty H, Dowe le RC, Strain JJ, Dunne A, Ward M, Molloy AM, et al. Riboflavin lowers homocysteine in individuals homozygous for the MTHFR 677C->T polymorphism. *Circulation* 2006;113(1):74-80.
- [229] Martin YN, Salavaggione OE, Eckloff BW, Wieben ED, Schaid DJ, Weinsilboum RM. Human methylenetetrahydrofolate reductase pharmacogenomics: gene resequencing and functional ge-

- nomics. *Pharmacogenet Genomics* 2006;16(4):265-77.
- [230] Selzer RR, Rosenblatt DS, Laxova R, Hogan K. Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. *N Engl J Med* 2003;349(1):45-50.
- [231] Hustad S, Ueland PM, Vollset SE, Zhang Y, Bjorke-Monsen AL, Schneede J. Riboflavin as a determinant of plasma total homocysteine: effect modification by the methylenetetrahydrofolate reductase C677T polymorphism. *Clin Chem* 2000;46(8 Pt 1):1065-71.
- [232] Suormala T, Gamse G, Fowler B. 5,10-Methylenetetrahydrofolate reductase (MTHFR) assay in the forward direction: residual activity in MTHFR deficiency. *Clin Chem* 2002;48(6 Pt 1):835-43.
- [233] Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. *Anesthesiology* 1988;68(2):213-16.
- [234] Nagele P, Zeugswetter B, Wiener C, Burger H, Hupfl M, Mittlbock M, et al. Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. *Anesthesiology* 2008;109(1):36-43.
- [235] Matsuzawa J, Matsui M, Konishi T, Noguchi K, Gur RC, Bilker W, et al. Age-related volumetric changes of brain gray and white matter in healthy infants and children. *Cereb Cortex* 2001;11(4):335-42.
- [236] Christensen B, Guttormsen AB, Schneede J, Riedel B, Refsum H, Svardal A, et al. Preoperative methionine loading enhances restoration of the cobalamin-dependent enzyme methionine synthase after nitrous oxide anesthesia. *Anesthesiology* 1994;80(5):1046-56.
- [237] Lin X, Lu D, Gao Y, Tao S, Yang X, Feng J, et al. Genome-wide association study identifies novel loci associated with serum level of vitamin B₁₂ in Chinese men. *Hum Mol Genet* 2012 Jun 1;21(11):2610-17.
- [238] Azevedo M, Eriksson S, Mendes N, Serpa J, Figueiredo C, Resende LP, et al. Infection by *Helicobacter pylori* expressing the BabA adhesin is influenced by the secretor phenotype. *J Pathol* 2008;215(3):308-16.
- [239] Oussalah A, Besseau C, Chery C, Jeannesson E, Gueant-Rodriguez RM, Anello G, et al. *Helicobacter pylori* serologic status has no influence on the association between fucosyltransferase 2 polymorphism (FUT2 461 G->A) and vitamin B-12 in Europe and West Africa. *Am J Clin Nutr* 2012;95(2):514-21.
- [240] Mollin DL, Baker SJ, Donlach I. Addisonian pernicious anaemia without gastric atrophy in a young man. *British Journal of Haematology* 1955;1(3):278-90.
- [241] Masnou H, Domenech E, Navarro-Llavat M, Zabana Y, Manosa M, Garcia-Planella E, et al. Pernicious anaemia in triplets. A case report and literature review. *Gastroenterologia y Hepatologia* 2007;30(10):580-2.
- [242] Cowan TM, Blitzer MG, Wolf B. Technical standards and guidelines for the diagnosis of biotinidase deficiency. *Genet Med* 2010;12(7):464-70.
- [243] Weber P, Scholl S, Baumgartner ER. Outcome in patients with profound biotinidase deficiency: relevance of newborn screening. *Develop Med Child Neurol* 2004;46(7):481-4.
- [244] Durance T. Residual Avid in Activity in Cooked Egg White Assayed with Improved Sensitivity. *Journal of Food Science* 1991;56(3):707-9.
- [245] Mock DM, Stratton SL, Horvath TD, Bogusiewicz A, Matthews NI, Henrich CL, et al. Urinary excretion of 3-hydroxyisovaleric acid and 3-hydroxyisovaleryl carnitine increases in response to a leucine challenge in marginally biotin-deficient humans. *J Nutr* 2011;141(11):1925-30.
- [246] Mock DM, Mock NI, Nelson RP, Lombard KA. Disturbances in biotin metabolism in children undergoing long-term anticonvulsant therapy. *J Pediatr Gastroenterol Nutr* 1998;26(3):245-50.
- [247] Fierce Y, de Morais Vieira M, Piantedosi R, Wyss A, Blaner WS, Paik J. In vitro and in vivo characterization of retinoid synthesis from beta-carotene. *Arch Biochem Biophys* 2008;472(2):126-38.
- [248] Ferrucci L, Perry JR, Matteini A, Perola M, Tanaka T, Silander K, et al. Common variation in the beta-carotene 15,150-monoxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. *Am J Hum Genet* 2009;84(2):123-33.
- [249] Lietz G, Oxley A, Leung W, Hesketh J. Single nucleotide polymorphisms upstream from the beta-carotene 15,150-monoxygenase gene influence provitamin A conversion efficiency in female

- volunteers. *J Nutr* 2012;142(1):161S-5S.
- [250] Amengual J, Lobo GP, Golczak M, Li HN, Klimova T, Hoppel CL, et al. A mitochondrial enzyme degrades carotenoids and protects against oxidative stress. *FASEB J* 2011;25(3):948-59.
- [251] Vage DI, Boman IA. A nonsense mutation in the beta-carotene oxygenase 2 (BCO2) gene is tightly associated with accumulation of carotenoids in adipose tissue in sheep (*Ovis aries*). *BMC Genet* 2010;11:10.
- [252] El Kares R, Manolescu DC, Lakhali-Chaieb L, Montpetit A, Zhang Z, Bhat PV, et al. A human ALDH1A2 gene variant is associated with increased newborn kidney size and serum retinoic acid. *Kidney Int* 2010;78(1):96-102.
- [253] Gilbert T, Merlet-Benichou C. Retinoids and nephron mass control. *Pediatr Nephrol* 2000;14(12):1137-44.
- [254] Zhang Z, Quinlan J, Hoy W, Hughson MD, Lemire M, Hudson T, et al. A common RET variant is associated with reduced newborn kidney size and function. *J Am Soc Nephrol* 2008;19(10):2027-34.
- [255] Clark AT, Bertram JF. Molecular regulation of nephron endowment. *Am J Physiol* 1999;276(4 Pt 2):F485-97.
- [256] Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertension* 1988;1(4 Pt 1):335-47.
- [257] Lindqvist A, Sharvill J, Sharvill DE, Andersson S. Loss-of-function mutation in carotenoid 15,150-monooxygenase identified in a patient with hypercarotenemia and hypovitaminosis A. *J Nutr* 2007;137(11):2346-50.
- [258] Cohen. Observations on carotenemia. *Ann Intern Med* 1958;48(2):219-27.
- [259] Sharvill DE. Familial hypercarotinaemia and hypovitaminosis A. *Proc R Soc Med* 1970;63(6):605-6.
- [260] Zhu J, Deluca HF, Vitamin D. 25-hydroxylase: Four decades of searching, are we there yet? *Arch Biochem Biophys* 2012 Jul 1;523(1):30e6.
- [261] Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. *Proc Natl Acad Sci U S A* 2004;101(20):7711-15.
- [262] Ramagopalan SV, Dyment DA, Cader MZ, Morrison KM, Disanto G, Morahan JM, et al. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. *Ann Neurol* 2011;70(6):881-6.
- [263] Huang J, Xie ZF. Polymorphisms in the vitamin D receptor gene and multiple sclerosis risk: A meta-analysis of case-control studies. *J Neurol Sci* 2012;313(1-2):79-85.
- [264] Jablonski NG, Chaplin G. Colloquium paper: human skin pigmentation as an adaptation to UV radiation. *Proc Natl Acad Sci U S A* 2010;107(Suppl. 2):8962-8.
- [265] Lalueza-Fox C, Rompler H, Caramelli D, Staubert C, Catalano G, Hughes D, et al. A melanocortin 1 receptor allele suggests varying pigmentation among Neanderthals. *Science* 2007;318(5855):1453-5.
- [266] Dessinioti C, Antoniou C, Katsambas A, Stratigos AJ. Melanocortin 1 receptor variants: functional role and pigmentary associations. *Photochem Photobiol* 2011;87(5):978-87.
- [267] Liu F, Struchalin MV, Duijn K, Hofman A, Uitterlinden AG, Duijn C, et al. Detecting low frequency loss-of-function alleles in genome wide association studies with red hair color as example. *PLoS One* 2011;6(11):e8145.
- [268] Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* 2010;376(9736):180-8.
- [269] McGrath JJ, Saha S, Burne TH, Eyles DW. A systematic review of the association between common single nucleotide polymorphisms and 25-hydroxyvitamin D concentrations. *J Steroid Biochem Mol Biol* 2010;121(1e2):471-7.
- [270] Fu L, Yun F, Oczak M, Wong BY, Vieth R, Cole DE. Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. *Clin Biochem* 2009;42(10e11):1174-7.

- [271] Ji GR, Yao M, Sun CY, Li ZH, Han Z. BsmI, TaqI, ApaI and FokI polymorphisms in the vitamin D receptor (VDR) gene and risk of fracture in Caucasians: a meta-analysis. *Bone* 2010;47(3):681-6.
- [272] Lee JE. Circulating levels of vitamin D, vitamin D receptor polymorphisms, and colorectal adenoma: a meta-analysis. *Nutr Res Pract* 2011;5(5):464-70.
- [273] Rollison DE, Cole AL, Tung KH, Slattery ML, Baumgartner KB, Byers T, et al. Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the southwestern. *US Breast Cancer Res Treat* 2012 Apr;132(2):683-91.
- [274] Kang TJ, Jin SH, Yeum CE, Lee SB, Kim CH, Lee SH, et al. Vitamin D Receptor Gene Taq I, BsmI and FokI polymorphisms in Korean patients with tuberculosis. *Immune Netw* 2011;11(5):253-7.
- [275] Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *N Engl J Med* 2011;365(5):410-21.
- [276] Pillai DK, Iqbal SF, Benton AS, Lerner J, Wiles A, Foerster M, et al. Associations between genetic variants in vitamin D metabolism and asthma characteristics in young African Americans: a pilot study. *J Invest Med* 2011;59(6):938-46.
- [277] Chardon L, Sassolas A, Digeon B, Michel-Calemard L, Bovier-Lapierre M, Moulin P, et al. Identification of two novel mutations and long-term follow-up in abetalipoproteinemia: a report of four cases. *Eur J Pediatr* 2009;168(8):983-9.
- [278] Zamel R, Khan R, Pollex RL, Hegele RA. Abetalipoproteinemia: two case reports and literature review. *Orphanet J Rare Dis* 2008;3:19.
- [279] Peretti N, Sassolas A, Roy CC, Deslandres C, Charcosset M, Castagnetti J, et al. Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers. *Orphanet J Rare Dis* 2010;5:24.
- [280] Gotoda T, Arita M, Arai H, Inoue K, Yokota T, Fukuo Y, et al. Adult-onset spinocerebellar dysfunction caused by a mutation in the gene for the alpha-tocopherol-transfer protein. *N Engl J Med* 1995;333(20):1313-18.
- [281] Bardowell SA, Stec DE, Parker RS. Common variants of cytochrome P450 4F2 exhibit altered vitamin E- ω -hydroxylase specific activity. *J Nutr* 2010;140(11):1901-6.
- [282] Jain V, Wood SJ, Feiveson AH, Black FO, Paloski WH. Diagnostic accuracy of dynamic posturography testing after short-duration spaceflight. *Aviat Space Environ Med* 2010;81(7):625-31.
- [283] Kohlmeier M, Salomon A, Saupe J, Shearer MJ. Transport of vitamin K to bone in humans. *J Nutr* 1996;126(Suppl. 4):1192S-6S.
- [284] Vermeer C. Vitamin K: the effect on health beyond coagulation and overview. *Food Nutr Res* 2012:56.
- [285] Kohlmeier M, Saupe J, Schaefer K, Asmus G. Bone fracture history and prospective bone fracture risk of hemodialysis patients are related to apolipoprotein E genotype. *Calcif Tissue Int* 1998;62(3):278-81.
- [286] Peter I, Crosier MD, Yoshida M, Booth SL, Cupples LA, Dawson-Hughes B, et al. Associations of APOE gene polymorphisms with bone mineral density and fracture risk: a meta-analysis. *Osteoporosis International* 2011;22(4):1199-209.
- [287] Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *Proc Natl Acad Sci U S A* 2005;102(44):16025-30.
- [288] Zeisel SH. Nutritional genomics: defining the dietary requirement and effects of choline. *J Nutr* 2011;141(3):531-4.
- [289] Song J, da Costa KA, Fischer LM, Kohlmeier M, Kwock L, Wang S, et al. Polymorphism of the PEMT gene and susceptibility to nonalcoholic fatty liver disease (NAFLD). *FASEB J* 2005;19(10):1266-71.
- [290] Johnson AR, Lao S, Wang T, Galanko JA, Zeisel SH. Choline Dehydrogenase Polymorphisms rs12676 Is a Functional Variation and Is Associated with Changes in Human Sperm Cell Function. *PLoS One* 2012;7(4):36047.

BÖLÜM 5

Nutrigenetik Uzun Süreli Sağlığı Nasıl Etkiler?

223

TERİMLER

- Epistaz: Beslenme genetik etkileşiminin başka bir lokusta varyasyon ile modifikasyonu.
- Hemizigosit: Bir genin olağan iki kopyasından sadece birinin hücrelerde bulunduğu durum.
- Nöral tüp defektleri: Anensefali, spina bifida ve ilişkili doğum kusurları.

ÖZET

Beslenme faktörleri, birçok yaygın durumların ve hastalıkların gelişiminde gelişen hastalıkların önlenmesinde ve tedavisinde eşit derecede önemli bir rol oynar. Genellikle beslenme faktörleri bazı bireylerde fark yaratırken diğer bireylerde fark yaratmaz. Beslenme metabolizmasında yer alan genlerin doğru bir şekilde anlaşılması ve beslenme durumlarının düzenlenmesi, sıklıkla ortak genetik varyantların önemli beslenme faktörlerine yanıtı nasıl değiştirdiğini anlamaya yardımcı olur. Bu bölüm, bu etkileşimlerin kaç tanesini bildiğimizi göstermek için karmaşık hastalıklar ve koşullar bağlamında nutrigenetik varyasyonu araştırmaktadır.

5.1 İYİ BESLENME FARKLI BİREYLER İÇİN FARKLI BESİNLER DEMEKTİR

Şimdi, beslenme seçimlerinin sağlık sonuçlarına etkisini ele alacağız. Tamamen aynı şeyleri tüketen iki bireyin sağlık sonuçları oldukça farklı olabilir. Bunun sebebi önceki bölümlerde açıkça belirtilmesi gerektiği gibi, her bireyin metabolizmasının genom tarafından farklı şekilde ayarlanmış olmasıdır. Sağlık koşullarının artmasıyla beslenme müdahalelerine bireylerin verdikleri cevapları tahmin edebilir ve bireysel tercihleri grafiklemek için genetik bilgileri kullanabiliriz. Bahsedilen gen-besin etkileşimlerinin çoğunun ek araştırmalarla

KAYNAKLAR

- [1] Zugna D, Richiardi L, Akre O, Stephansson O, Ludvigsson JF. A nationwide population-based study to determine whether coeliac disease is associated with infertility. *Gut* 2010;59(11): 1471-5.
- [2] Zugna D, Richiardi L, Akre O, Stephansson O, Ludvigsson JF. Celiac disease is not a risk factor for infertility in men. *Fertil Steril* 2011;95(5):1709e13. e1-3.
- [3] Rosenfeld CS, Roberts RM. Maternal diet and other factors affecting offspring sex ratio: a review. *Biol Reprod* 2004;71(4):1063-70.
- [4] Villamor E, Sparen P, Cnattingius S. Interpregnancy weight gain and the male-to-female sex ratio of the second pregnancy: a population-based cohort study. *Fertil Steril* 2008;89(5): 1240-4.
- [5] Ahrens K, Yazdy MM, Mitchell AA, Werler MM. Folic acid intake and spina bifida in the era of dietary folic acid fortification. *Epidemiology* 2011;22(5):731-7.
- [6] Shaw GM, Lu W, Zhu H, Yang W, Briggs FB, Carmichael SL, et al. 118 SNPs of folate-related genes and risks of spina bifida and conotruncal heart defects. *BMC Med Genet* 2009;10:49.
- [7] Hustad S, Ueland PM, Vollset SE, Zhang Y, Bjorke-Monsen AL, Schneede J. Riboflavin as a determinant of plasma total homocysteine: effect modification by the methylenetetrahydrofolate reductase C677T polymorphism. *Clin Chem* 2000;46(8 Pt 1):1065-71.
- [8] Moat SJ, Ashfield-Watt PA, Powers HJ, Newcombe RG, McDowell IF. Effect of riboflavin status on the homocysteine-lowering effect of folate in relation to the MTHFR (C677T) genotype. *Clin Chem* 2003;49(2):295-302.
- [9] Finnell RH, Shaw GM, Lammer EJ, Rosenquist TH. Gene-nutrient interactions: importance of folic acid and vitamin B₁₂ during early embryogenesis. *Food Nutr Bull* 2008; 29(Suppl. 2):S86e98. discussion S99-100.
- [10] Zeisel SH. Nutritional genomics: defining the dietary requirement and effects of choline. *J Nutr* 2011;141(3):531-4.
- [11] Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol* 2004; 160(2):102-9.
- [12] Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *Proc Natl Acad Sci U S A* 2005;102(44):16025-30.
- [13] Parle-McDermott A, Kirke PN, Mills JL, Molloy AM, Cox C, O'Leary VB, et al. Confirmation of the R653Q polymorphism of the trifunctional C1-synthase enzyme as a maternal risk for neural tube defects in the Irish population. *Eur J Hum Genet* 2006;14(6):768-72.
- [14] Johnson WG, Scholl TO, Spychala JR, Buyske S, Stenroos ES, Chen X. Common dihydrofolate reductase 19-base pair deletion allele: a novel risk factor for preterm delivery. *Am J Clin Nutr* 2005;81(3):664-8.
- [15] Siega-Riz AM, Promislow JH, Savitz DA, Thorp Jr JM, McDonald T. Vitamin C intake and the risk of preterm delivery. *Am J Obstet Gynecol* 2003;189(2):519-25.
- [16] Erichsen HC, Engel SA, Eck PK, Welch R, Yeager M, Levine M, et al. Genetic variation in the sodium-dependent vitamin C transporters, SLC23A1, and SLC23A2 and risk for preterm delivery. *Am J Epidemiol* 2006;163(3):245-54.
- [17] Innis SM, King DJ. trans Fatty acids in human milk are inversely associated with concentrations of essential all-cis n-6 and n-3 fatty acids and determine trans, but not n-6 and n-3, fatty acids in plasma lipids of breast-fed infants. *Am J Clin Nutr* 1999;70(3):383-90.
- [18] Guesnet P, Alessandri JM. Docosahexaenoic acid (DHA) and the developing central nervous system (CNS) implications for dietary recommendations. *Biochimie* 2011;93(1):7-12.
- [19] Cheatham CL, Nerhammer AS, Asserhoj M, Michaelsen KF, Lauritzen L. Fish oil supplementation during lactation: effects on cognition and behavior at 7 years of age. *Lipids* 2011;46(7):637-45.
- [20] Xie L, Innis SM. Genetic variants of the FADS1 FADS2 gene cluster are associated with altered

- (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. *J Nutr* 2008;138(11):2222-8.
- [21] Luka Z, Moss F, Loukachevitch LV, Bornhop DJ, Wagner C. Histone demethylase LSD1 is a folate-binding protein. *Biochemistry* 2011;50(21):4750-6.
- [22] Zeisel SH. Dietary choline deficiency causes DNA strand breaks and alters epigenetic marks on DNA and histones. *Mutat Res* 2012;733(1e2):34-8.
- [23] Xu X, Gammon MD, Wetmur JG, Rao M, Gaudet MM, Teitelbaum SL, et al. A functional 19-base pair deletion polymorphism of dihydrofolate reductase (DHFR) and risk of breast cancer in multivitamin users. *Am J Clin Nutr* 2007;85(4):1098-102.
- [24] Maruti SS, Ulrich CM, Jupe ER, White E. MTHFR C677T and postmenopausal breast cancer risk by intakes of one-carbon metabolism nutrients: a nested case-control study. *Breast Cancer Research: BCR* 2009;11(6):R91.
- [25] Haslacher H, Perkmann T, Gruenewald J, Exner M, Endler G, Scheichenberger V, et al. Plasma myeloperoxidase level and peripheral arterial disease. *Eur J Clin Invest* 2012;42(5):463-9.
- [26] Ahn J, Gammon MD, Santella RM, Gaudet MM, Britton JA, Teitelbaum SL, et al. Myeloperoxidase genotype, fruit and vegetable consumption, and breast cancer risk. *Cancer Res* 2004;64(20):7634-9.
- [27] Schallreuter KU, Salem MM, Hasse S, Rokos H. The redoxbiochemistry of human hair pigmentation. *Pigment Cell & Melanoma Research* 2011;24(1):51-62.
- [28] Nadif R, Mintz M, Jedlicka A, Bertrand JP, Kleeberger SR, Kauffmann F. Association of CAT polymorphisms with catalase activity and exposure to environmental oxidative stimuli. *Free Radical Research* 2005;39(12):1345-50.
- [29] Ahn J, Gammon MD, Santella RM, Gaudet MM, Britton JA, Teitelbaum SL, et al. Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use. *Am J Epidemiol* 2005;162(10):943-52.
- [30] Saracino MR, Lampe JW. Phytochemical regulation of UDP-glucuronosyltransferases: implications for cancer prevention. *Nutrition and Cancer* 2007;59(2):121-41.
- [31] Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, et al. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev* 2008;17(1):39-47.
- [32] Lilla C, Verla-Tebit E, Risch A, Jager B, Hoffmeister M, Brenner H, et al. Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev* 2006;15(1):99-107.
- [33] Hiljadnikova Bajro M, Josifovski T, Panovski M, Jankulovski N, Kapedanovska Nestorovska A, Matevska N, et al. Promoter length polymorphism in UGT1A1 and the risk of sporadic colorectal cancer. *Cancer Genetics* 2012;205(4):163-7.
- [34] Chang JL, Bigler J, Schwarz Y, Li SS, Li L, King IB, et al. UGT1A1 polymorphism is associated with serum bilirubin concentrations in a randomized, controlled, fruit and vegetable feeding trial. *J Nutr* 2007;137(4):890-7.
- [35] Gervasini G, San Jose C, Carrillo JA, Benitez J, Cabanillas A. GST polymorphisms interact with dietary factors to modulate lung cancer risk: study in a high-incidence area. *Nutrition and Cancer* 2010;62(6):750-8.
- [36] Shen J, Gammon MD, Terry MB, Wang L, Wang Q, Zhang F, et al. Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2005;14(2):336-42.
- [37] Goodman M, Bostick RM, Ward KC, Terry PD, van Gils CH, Taylor JA, et al. Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. *Nutrition Cancer* 2006;55(1):13-20.
- [38] Shen J, Terry MB, Gammon MD, Gaudet MM, Teitelbaum SL, Eng SM, et al. MGMT genotype modulates the associations between cigarette smoking, dietary antioxidants and breast cancer risk. *Carcinogenesis* 2005;26(12):2131-7.

- [39] Eylert MF, Persad R. Management of prostate cancer. *Br J Hosp Med (Lond)* 2012;73(2):95-9.
- [40] Hedelin M, Balter KA, Chang ET, Bellocco R, Klint A, Johansson JE, et al. Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006;66(14):1512-20.
- [41] Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Preventive Medicine* 1990;19(6):614-22.
- [42] Anderson LN, Cotterchio M, Cole DE, Knight JA. Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among Caucasian women in Ontario. *Cancer Epidemiol Biomarkers Prev* 2011;20(8):1708-17.
- [43] Kaseda R, Hosojima M, Sato H, Saito A. Role of megalin and cubilin in the metabolism of vitamin D(3). *Therapeutic Apheresis Dialysis* 2011;15(Suppl. 1):14-17.
- [44] Abrams SA, Griffin IJ, Hawthorne KM, Chen Z, Gunn SK, Wilde M, et al. Vitamin D receptor FokI polymorphisms affect calcium absorption, kinetics, and bone mineralization rates during puberty. *Journal Bone Mineral Research* 2005;20(6):945-53.
- [45] Slattery ML, Wolff RK, Herrick JS, Caan BJ, Samowitz W. Calcium, vitamin D, VDR genotypes, and epigenetic and genetic changes in rectal tumors. *Nutrition Cancer* 2010;62(4): 436-42.
- [46] Hedelin M, Chang ET, Wiklund F, Bellocco R, Klint A, Adolfsson J, et al. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. *Int J Cancer* 2007;120(2):398-405.
- [47] Gouda HN, Sagoo GS, Harding AH, Yates J, Sandhu MS, Higgins JP. The association between the peroxisome proliferator-activated receptor-gamma2 (PPARG2) Pr012Ala gene variant and type 2 diabetes mellitus: a HuGE review and meta-analysis. *Am J Epidemiol* 2010;171(6): 645-55.
- [48] Nettleton JA, McKeown NM, Kanoni S, Lemaitre RN, Hivert MF, Ngwa J, et al. Interactions of dietary whole-grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies. *Diabetes Care* 2010;33(12): 2684-91.
- [49] Ruchat SM, Elks CE, Loos RJ, Vohl MC, Weisnagel SJ, Rankinen T, et al. Evidence of interaction between type 2 diabetes susceptibility genes and dietary fat intake for adiposity and glucose homeostasis-related phenotypes. *Journal of Nutrigenetics Nutrigenomics* 2009; 2(4e5):225-34.
- [50] Herranz D, Serrano M. SIRT1: recent lessons from mouse models. *Nat Rev Cancer* 2010; 10(12):819-23.
- [51] Zillikens MC, van Meurs JB, Sijbrands EJ, Rivadeneira F, Dehghan A, van Leeuwen JP, et al. SIRT1 genetic variation and mortality in type 2 diabetes: interaction with smoking and dietary niacin. *Free Radic Biol Med* 2009;46(6):836-41.
- [52] Sarkkinen E, Korhonen M, Erkkila A, Ebeling T, Uusitupa M. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *Am J Clin Nutr* 1998;68(6):1215-22.
- [53] Wolff E, Vergnes MF, Defoort C, Planells R, Portugal H, Nicolay A, et al. Cholesterol absorption status and fasting plasma cholesterol are modulated by the microsomal triacylglycerol transfer protein -493 G/T polymorphism and the usual diet in women. *Genes Nutr* 2011;6(1):71-9.
- [54] Ordovas JM, Lopez-Miranda J, Mata P, Perez-Jimenez F, Lichtenstein AH, Schaefer EJ. Gene-diet interaction in determining plasma lipid response to dietary intervention. *Atherosclerosis* 1995;118(Suppl.):S11-27. 266 *Nutrigenetics*
- [55] Ordovas JM. Gene-diet interaction and plasma lipid responses to dietary intervention. *Biochemical Society Transactions* 2002;30(2):68-73.
- [56] Dumont J, Huybrechts I, Spinneker A, Gottrand F, Grammatikaki E, Bevilacqua N, et al. FADS1 genetic variability interacts with dietary alpha-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. *J Nutr* 2011;141(7):1247-53.
- [57] Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, et al. 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(1):38-46.

- [58] Rantala M, Rantala TT, Savolainen MJ, Friedlander Y, Kesaniemi YA. Apolipoprotein B gene polymorphisms and serum lipids: meta-analysis of the role of genetic variation in responsiveness to diet. *Am J Clin Nutr* 2000;71(3):713-24.
- [59] Clarke R, Bennett DA, Parish S, Verhoef P, Dotsch-Klerk M, Lathrop M, et al. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. *PLoS Med* 2012;9(2):-1001177.
- [60] Wilson CP, Ward M, McNulty H, Strain JJ, Trouton TG, Horigan G, et al. Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow-up. *Am J Clin Nutr* 2012;95(3):766-72.
- [61] Sofi F, Conti AA, Gori AM, Eliana Luisi ML, Casini A, Abbate R, et al. Coffee consumption and risk of coronary heart disease: a meta-analysis. *Nutrition, metabolism, and cardiovascular diseases: NMCD* 2007;17(3):209-23.
- [62] Rasmussen BB, Brix TH, Kyvik KO, Brosen K. The interindividual differences in the 3-demethylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. *Pharmacogenetics* 2002;12(6):473-8.
- [63] Cornelis MC, El-Sohehy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA* 2006;295(10):1135-41.
- [64] Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med* 2001;345(11):779-83.
- [65] Bartholomew JR, Schaffer JL, McCormick GF. Air travel and venous thromboembolism: minimizing the risk. *Cleve Clin J Med* 2011;78(2):111-20.
- [66] Lilienfeld DE. Decreasing mortality from pulmonary embolism in the United States, 1979-1996. *Int J Epidemiol* 2000;29(3):465-9.
- [67] Ceelie H, Spaargaren-van Riel CC, Bertina RM, Vos HL. G20210A is a functional mutation in the prothrombin gene; effect on protein levels and 30-end formation. *J Thromb Haemost* 2004;2(1):119-27.
- [68] Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, Buring JE. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. *Circulation* 2007;116(13):1497-503.
- [69] Zee RY, Glynn RJ, Cheng S, Steiner L, Rose L, Ridker PM. An evaluation of candidate genes of inflammation and thrombosis in relation to the risk of venous thromboembolism: The Women's Genome Health Study. *Circ Cardiovasc Genet* 2009;2(1):57-62.
- [70] Bezemer ID, Bare LA, Arellano AR, Reitsma PH, Rosendaal FR. Updated analysis of gene variants associated with deep vein thrombosis. *JAMA* 2010;303(5):421-2.
- [71] Peden DB. The role of oxidative stress and innate immunity in O(3) and endotoxin-induced human allergic airway disease. *Immunol Rev* 2011;242(1):91-105.
- [72] Versari D, Daghini E, Rodriguez-Porcel M, Sattler K, Galili O, Pilarczyk K, et al. Chronic antioxidant supplementation impairs coronary endothelial function and myocardial perfusion in normal pigs. *Hypertension* 2006;47(3):475-81.
- [73] Romieu I, Sienna-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. *Thorax* 2004;59(1):8-10.
- [74] Romieu I, Mannino DM, Redd SC, McGeehin MA. Dietary intake, physical activity, body mass index, and childhood asthma in the Third National Health And Nutrition Survey (NHANES III). *Pediatr Pulmonol* 2004;38(1):31-42. *Health Effects CHAPTER 5* 267
- [75] Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;127(3):724-33.
- [76] Dickens C. *Bleak House, Chapter XVI, Tom-All-Alone's*. London: Bradbury & Evans. Transcript of the UNC copy can be found at, <http://www.ibiblio.org/dickens/html/42049.html>; 1852. p.155.
- [77] Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its

evolutionary implications. *Mol Biol Evol* 2002;19(5):640-53.

- [78] Johnson RJ, Andrews P, Benner SA, Oliver W, Theodore E. Woodward award. The evolution of obesity: insights from the mid-Miocene. *Trans Am Clin Climatol Assoc* 2010; 121:295-305. discussion 308.
- [79] Le MT, Shafiu M, Mu W, Johnson RJ. SLC2A9 da fructose transporter identified as a novel uric acid transporter. *Nephrol Dial Transplant* 2008;23(9):2746-9.
- [80] Cheeseman C. Solute carrier family 2, member 9 and uric acid homeostasis. *Curr Opin Nephrol Hypertens* 2009;18(5):428-32.
- [81] Woodward OM, Kottgen A, Coresh J, Boerwinkle E, Guggino WB, Kottgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci U S A* 2009;106(25):10338-42.
- [82] Jutabha P, Anzai N, Kitamura K, Taniguchi A, Kaneko S, Yan K, et al. Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. *J Biol Chem* 2010;285(45):35123-32.
- [83] Meotti FC, Jameson GN, Turner R, Harwood DT, Stockwell S, Rees MD, et al. Urate as a physiological substrate for myeloperoxidase: implications for hyperuricemia and inflammation. *J Biol Chem* 2011;286(15):12901-11.
- [84] Puig JG, Michan AD, Jimenez ML, Perez de Ayala C, Mateos FA, Capitan CF, et al. Female gout. Clinical spectrum and uric acid metabolism. *Arch Intern Med* 1991;151(4):726-32.
- [85] Fujimori S, Hidaka Y, Davidson BL, Palella TD, Kelley WN. Identification of a single nucleotide change in a mutant gene for hypoxanthine-guanine phosphoribosyltransferase (HPRT). *Hum Genet* 1988;79(1):39-43.
- [86] Davidson BL, Pashmforoush M, Kelley WN, Palella TD. Human hypoxanthine-guanine phosphoribosyltransferase deficiency. The molecular defect in a patient with gout (HPRT-Ashville). *J Biol Chem* 1989;264(1):520-5.
- [87] Nguyen KV, Naviaux RK, Paik KK, Nyhan WL. Novel Mutations in the Human HPRT Gene. *Nucleosides Nucleotides Nucleic Acids* 2011;30(6):440-5.
- [88] Ea HK, Bardin T, Jinnah HA, Aral B, Liote F, Ceballos-Picot I. Severe gouty arthritis and mild neurologic symptoms due to F199C, a newly identified variant of the hypoxanthine guanine phosphoribosyltransferase. *Arthritis Rheum* 2009;60(7):2201-4.
- [89] Phipps-Green AJ, Hollis-Moffatt JE, Dalbeth N, Merriman ME, Topless R, Gow PJ, et al. A strong role for the ABCG2 gene in susceptibility to gout in New Zealand Pacific Island and Caucasian, but not Maori, case and control sample sets. *Hum Mol Genet* 2010;19(24):4813-9.
- [90] Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 2010;3(6):523-30.
- [91] Tu HP, Chen CJ, Tovosia S, Ko AM, Lee CH, Ou TT, et al. Associations of a non-synonymous variant in SLC2A9 with gouty arthritis and uric acid levels in Han Chinese subjects and Solomon Islanders. *Ann Rheum Dis* 2010;69(5):887-90.
- [92] Stark K, Reinhard W, Grassl M, Erdmann J, Schunkert H, Illig T, et al. Common polymorphisms influencing serum uric acid levels contribute to susceptibility to gout, but not to coronary artery disease. *PLoS One* 2009;4(11):-7729.
- [93] Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* 2009;5(6):-1000504.
- [94] Cea Soriano L, Rothenbacher D, Choi HK, Garcia Rodriguez LA. Contemporary epidemiology of gout in the UK general population. *Arthritis Res Ther* 2011;13(2):R39.
- [95] Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA* 2010;304(20):2270e8. 268 Nutrigenetics
- [96] Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 2004;350(11):1093-103.
- [97] Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study.

- Arch Intern Med 2009;169(5):502-7.
- [98] Juraschek SP, Miller 3rd ER, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: A meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken)* 2011 Sep;63(9):1295-306.
- [99] Rose BS. Gout in Maoris. *Semin Arthritis Rheum* 1975;5(2):121-45.
- [100] Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis* 1997;56(1):22-6.
- [101] Hollis-Moffatt JE, Xu X, Dalbeth N, Merriman ME, Topless R, Waddell C, et al. Role of the urate transporter SLC2A9 gene in susceptibility to gout in New Zealand Maori, Pacific Island, and Caucasian case-control sample sets. *Arthritis Rheum* 2009; 60(11):3485-92.
- [102] Simmonds HA, McBride MB, Hatfield PJ, Graham R, McCaskey J, Jackson M. Polynesian women are also at risk for hyperuricaemia and gout because of a genetic defect in renal urate handling. *Br J Rheumatol* 1994;33(10):932-7.
- [103] Hollis-Moffatt JE, Gow PJ, Harrison AA, Highton J, Jones PB, Stamp LK, et al. The SLC2A9 nonsynonymous Arg265His variant and gout: evidence for a population-specific effect on severity. *Arthritis Res Ther* 2011;13(3):R85.
- [104] Manini TM, Patel KV, Bauer DC, Ziv E, Schoeller DA, Mackey DC, et al. European ancestry and resting metabolic rate in older African Americans. *Eur J Clin Nutr* 2011;65(6):663-7.
- [105] Nagai N, Sakane N, Tsuzaki K, Moritani T. UCP1 genetic polymorphism (-3826 A/G) diminishes resting energy expenditure and thermoregulatory sympathetic nervous system activity in young females. *Int J Obes (Lond)* 2011;35(8):1050-5.
- [106] Martinez-Hervas S, Mansego ML, de Marco G, Martinez F, Alonso MP, Morcillo S, et al. Polymorphisms of the UCP2 gene are associated with body fat distribution and risk of abdominal obesity in Spanish population. *Eur J Clin Invest* 2012;42(2):171-8.
- [107] Jia JJ, Tian YB, Cao ZH, Tao LL, Zhang X, Gao SZ, et al. The polymorphisms of UCP1 genes associated with fat metabolism, obesity and diabetes. *Molecular Biology Reports* 2010;37(3):1513-22.
- [108] Herrmann SM, Wang JG, Staessen JA, Kertmen E, Schmidt-Petersen K, Zidek W, et al. Uncoupling protein 1 and 3 polymorphisms are associated with waist-to-hip ratio. *J Mol Med (Berl)* 2003;81(5):327-32.
- [109] Martinez-Hervas S, Mansego ML, de Marco G, Martinez F, Alonso MP, Morcillo S, et al. Polymorphisms of the UCP2 gene are associated with body fat distribution and risk of abdominal obesity in Spanish population. *Eur J Clin Invest* 2012;42(2):171-8.
- [110] Dalgaard LT. Genetic Variance in Uncoupling Protein 2 in Relation to Obesity, Type 2 Diabetes, and Related Metabolic Traits: Focus on the Functional -866G>A Promoter Variant (rs659366). *Journal of Obesity* 2011;2011:340241.
- [111] de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Conde R. Association of -55ct Polymorphism of Ucp3 Gene with Fat Distribution, Cardiovascular Risk Factors and Adipocytokines in Patients with Type 2 Diabetes Mellitus. *Journal Endocrinological Investigation* 2012;35(7):625-8.
- [112] Kubaszek A, Pihlajamaki J, Punnonen K, Karhapaa P, Vauhkonen I, Laakso M. The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes* 2003;52(2):558-61.
- [113] Di Renzo L, Carbonelli MG, Bianchi A, Iacopino L, Fiorito R, Di Daniele N, et al. Body composition changes after laparoscopic adjustable gastric banding: what is the role of -174G>C interleukin-6 promoter gene polymorphism in the therapeutic strategy? *Int J Obes (Lond)* 2012;36(3):369-78.
- [114] Vink JM, Boomsma DI, Medland SE, de Moor MH, Stubbe JH, Cornes BK, et al. Variance components models for physical activity with age as modifier: a comparative twin study in seven countries. *Twin Res Hum Genet* 2011;14(1):25-34. *Health Effects* CHAPTER 5 269
- [115] De Moor MH, Liu YJ, Boomsma DI, Li J, Hamilton JJ, Hottenga JJ, et al. Genome-wide association study of exercise behavior in Dutch and American adults. *Med Sci Sports Exerc*

2009;41(10):1887-95.

- [116] Pooley EC, Fairburn CG, Cooper Z, Sodhi MS, Cowen PJ, Harrison PJ. A 5-HT_{2C} receptor promoter polymorphism (HTR2Cd759C/T) is associated with obesity in women, and with resistance to weight loss in heterozygotes. *American journal of medical genetics Part B, Neuropsychiatric Genetics: the official publication of the International Society of Psychiatric Genetics* 2004;126B(1):124-7.
- [117] Phillips CM, Kesse-Guyot E, McManus R, Hercberg S, Lairon D, Planells R, et al. High dietary saturated fat intake accentuates obesity risk associated with the fat mass and obesity-associated gene in adults. *J Nutr* 2012;142(5):824-31.
- [118] McCaffery JM, Papandonatos GD, Peter I, Huggins GS, Raynor HA, Delahanty LM, et al. Obesity susceptibility loci and dietary intake in the Look AHEAD Trial. *Am J Clin Nutr* 2012 Jun;95(6):1477-86.
- [119] Sarzynski MA, Jacobson P, Rankinen T, Carlsson B, Sjostrom L, Bouchard C, et al. Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. *Int J Obes (Lond)* 2011;35(5):676-83.
- [120] Molerés A, Ochoa MC, Rendo-Urteaga T, Martínez-González MA, Azcona San Julian MC, Martínez JA, et al. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children. *Br J Nutr* 2012;107(4):533-8.
- [121] Qi L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. *Hum Mol Genet* 2008;17(22):3502-8.
- [122] Bedi G, Foltin RW, Gunderson EW, Rabkin J, Hart CL, Comer SD, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology (Berl)* 2010;212(4):675-86.
- [123] Bienertova-Vasku J, Bienert P, Slovackova L, Sabilkova L, Piskackova Z, Forejt M, Spichal Z, Zlamal F, Vasku A. Variability in CNR1 locus influences protein intake and smoking status in the Central-European population. *Nutritional Neuroscience* 2012;15(4): 163-70.
- [124] Peeters A, Beckers S, Mertens I, Van Hul W, Van Gaal L. The G1422A variant of the cannabinoid receptor gene (CNR1) is associated with abdominal adiposity in obese men. *Endocrine* 2007;31(2):138-41.
- [125] Flanagan JM, Gerber AL, Cadet JL, Beutler E, Sipe JC. The fatty acid amide hydrolase 385 A/A (P129T) variant: haplotype analysis of an ancient missense mutation and validation of risk for drug addiction. *Hum Genet* 2006;120(4):581-8.
- [126] de Luis DA, Sagrado MG, Aller R, Izaola O, Conde R, Romero E. C358A missense polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase (FAAH) and insulin resistance in patients with diabetes mellitus type 2. *Diabetes Research Clinical Practice* 2010;88(1):76-80.
- [127] Ren D, Zhou Y, Morris D, Li M, Li Z, Rui L. Neuronal SH2B1 is essential for controlling energy and glucose homeostasis. *J Clin Invest* 2007;117(2):397-406.
- [128] Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, Tucker K, et al. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. *Arch Intern Med* 2009;169(20):1897-906.
- [129] Fryirs MA, Barter PJ, Appavoo M, Tuch BE, Tabet F, Heather AK, et al. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. *Arteriosclerosis Thrombosis Vascular Biology* 2010;30(8):1642-8.
- [130] Smith CE, Ordovas JM, Sanchez-Moreno C, Lee YC, Garaulet M. Apolipoprotein A-II polymorphism: relationships to behavioural and hormonal mediators of obesity. *Int J Obes (Lond)* 2012;36(1):130-6.
- [131] Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, Tsai MY, et al. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am J Clin Nutr* 2009;90(6):1466-75. 270 Nutrigenetics

- [132] Garaulet M, Corbalan MD, Madrid JA, Morales E, Baraza JC, Lee YC, et al. CLOCK gene is implicated in weight reduction in obese patients participating in a dietary programme based on the Mediterranean diet. *Int J Obes (Lond)* 2010;34(3):516-23.
- [133] Moleres A, Ochoa MC, Rendo-Urteaga T, Martinez-Gonzalez MA, Azcona San Julian MC, Martinez JA, et al. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish casecontrol study of children. *Br J Nutr* 2012;107(4):533-8.
- [134] Corella D, Qi L, Sorli JV, Godoy D, Portoles O, Coltell O, et al. Obese subjects carrying the 11482G>A polymorphism at the perilipin locus are resistant to weight loss after dietary energy restriction. *J Clin Endocrinol Metab* 2005;90(9):5121-6.
- [135] Nischalke HD, Berger C, Luda C, Berg T, Muller T, Grunhage F, et al. The PNPLA3 rs738409 148M/M genotype is a risk factor for liver cancer in alcoholic cirrhosis but shows no or weak association in hepatitis C cirrhosis. *PLoS One* 2011;6(11):-27087.
- [136] Sevastianova K, Kotronen A, Gastaldelli A, Perttila J, Hakkarainen A, Lundbom J, et al. Genetic variation in PNPLA3 (adiponutrin) confers sensitivity to weight loss-induced decrease in liver fat in humans. *Am J Clin Nutr* 2011;94(1):104-11.
- [137] Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D. Genome-wide association with bone mass and geometry in the Framingham Heart Study. *BMC Med Genet* 2007;8(Suppl. 1):S14.
- [138] Obermayer-Pietsch BM, Bonelli CM, Walter DE, Kuhn RJ, Fahrleitner-Pammer A, Berghold A, et al. Genetic predisposition for adult lactose intolerance and relation to diet, bone density, and bone fractures. *J Bone Min Res* 2004;19(1):42-7.
- [139] Tolonen S, Laaksonen M, Mikkila V, Sievanen H, Mononen N, Rasanen L, et al. Lactase gene c/t(-13910) polymorphism, calcium intake, and pQCT bone traits in Finnish adults. *Calcif Tissue Int* 2011;88(2):153-61.
- [140] Chatzipapas C, Boikos S, Drosos GI, Kazakos K, Tripsianis G, Serbis A, et al. Polymorphisms of the vitamin D receptor gene and stress fractures. *Horm Metab Res* 2009;41(8):635-40.
- [141] Casas JP, Bautista LE, Humphries SE, Hingorani AD. Endothelial nitric oxide synthase genotype and ischemic heart disease: meta-analysis of 26 studies involving 23028 subjects. *Circulation* 2004;109(11):1359-65.
- [142] Hillermann R, Carelse K, Gebhardt GS. The Glu298Asp variant of the endothelial nitric oxide synthase gene is associated with an increased risk for abruptio placentae in pre-eclampsia. *J Human Genetics* 2005;50(8):415-9.
- [143] George TW, Waroonphan S, Niwat C, Gordon MH, Lovegrove JA. The Glu298Asp single nucleotide polymorphism in the endothelial nitric oxide synthase gene differentially affects the vascular response to acute consumption of fruit and vegetable puree based drinks. *Molecular Nutrition Food Res* 2012;56(7):1014-24.

BÖLÜM 6

Son Bulguların Ne Anlama Geldiğini Nasıl Bilebiliriz?

273

TERİMLER

- Alel: Bir lokusta bulunan DNA dizileri.
- Otozomal: Sayılı kromozomların birinin kalıtsallıkla ilişkisi.
- Kodominant: İki özelliğin aynı anda görülebildiği kalıtım durumu.
- Uyum: Kardeşler arasında bir özellik veya fenotipin benzerlik derecesi.
- Eş segregasyon: Kişisel özelliklerin veya lokusların birlikte kalıtsallık eğilimi.
- Baskın: Özelliğin her zaman heterozigot durumdaki diğer (çekinik) özelliği geçersiz kıldığı kalıtım durumu.
- Epistaz: Bir lokusun uzak bir lokusta özelliklerin görünümünü etkilediği yer.
- Genotip: Kalıtsal varyantların bir gen lokusunda kombinasyonu.
- Knock-in modeli: Hedeflenen genom dizisinin değiştirilmesiyle oluşan hayvanın suşu.
- Knockout modeli: Bir genin hedefe yönelik silinmesi ile oluşan hayvanın suşu.
- Bağlantı dengesizliği: İki alelin veya lokusun istatistiksel ilişkisi.
- LoD skoru: Olasılıkların logaritması; iki özellik veya lokus arasındaki mesafenin ölçüsü.
- Mendel randomizasyonu: Sonuçların genotip ile karşılaştırıldığı bir çalışma tasarımı.
- Monozigotik ikizler: Aynı döllenmiş yumurtadan yetiştirilen kardeşler.
- Fenotip: Dış veya biyolojik görünüm.
- QTL: Niceliksel özellik lokusu (çoğul lokus).
- Resesif: Özelliğin heterozigot durumdaki diğer (baskın) özellik tarafından daima geçersiz kıldığı kalıtım durumu.
- Segregasyon (İrk) analizi: Nesiller boyunca özellik oranlarının incelenmesi.

ÖZET

Nutrigenetik bulguların, sonuçların ve hipotezlerin geçerliliğini ve uygunluğunu değerlendirmek için ilk ön koşul, yaygın olarak kullanılan araştırma yöntemlerini anlamaktır. İn vitro çalışmalar, hayvan deneyleri, popülasyon çalışmaları ve klinik araştırmalar hakkında bir rapor labirentinde ilerlemelisiniz. Genetikçiler, genetik olarak değiştirilmiş hü-

ve yorumsal hatalar her zaman kafamızı karıştırmak için komplo kuruyor. Bu potansiyel sorunların farkında olmak, bildirilen bulguları perspektifte tutmamıza yardımcı olacaktır. En önemlisi, kritik kararlar almak için ilk bulgulara güvenilmesinden önce hastanın yeniden değerlendirilmesi ve tekrarlanmasıdır. Şimdi, kanıtların yeterince güçlü olduğunu varsayalım, ama pratikte öyle mi? Bir sonraki bölüm, gelecek vaat eden nutrigenetik kombinasyonların gerçek kullanım potansiyelini araştıracaktır.

KAYNAKLAR

- [1] Sofi F, Conti AA, Gori AM, Eliana Luisi ML, Casini A, Abbate R, et al. Coffee consumption and risk of coronary heart disease: a meta-analysis. *Nutrition, metabolism, and cardiovascular diseases: NMCD* 2007;17(3):209-23.
- [2] Cornelis MC, El-Soheily A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA* 2006;295(10):1135-41.
- [3] Fernandez-Canon JM, Granadino B, Beltran-Valero de Bernabe D, Renedo M, FernandezRuiz E, Penalva MA, et al. The molecular basis of alkaptonuria. *Nat Genet* 1996;14(1):19-24.
- [4] Martin YN, Salavaggione OE, Eckloff BW, Wieben ED, Schaid DJ, Weinshilboum RM. Human methylenetetrahydrofolate reductase pharmacogenomics: gene resequencing and functional genomics. *Pharmacogenet Genomics* 2006;16(4):265-77.
- [5] Zarse K, Schmeisser S, Birringer M, Falk E, Schmoll D, Ristow M. Differential effects of resveratrol and SRT1720 on lifespan of adult *Caenorhabditis elegans*. *Horm Metab Res* 2010;42(12):837-9.
- [6] Zheng D, Feeney GP, Kille P, Hogstrand C. Regulation of ZIP and ZnT zinc transporters in zebrafish gill: zinc repression of ZIP10 transcription by an intronic MRE cluster. *Physiol Genomics* 2008;34(2):205-14.
- [7] Shimano H. Novel qualitative aspects of tissue fatty acids related to metabolic regulation: Lessons from Elov16 knockout. *Prog Lipid Res* 2012;51(3):267-71.
- [8] Sullivan PM, Mezdoor H, Aratani Y, Knouff C, Najib J, Reddick RL, et al. Targeted replacement of the mouse apolipoprotein E gene with the common human APOE3 allele enhances diet-induced hypercholesterolemia and atherosclerosis. *J Biol Chem* 1997;272(29):17972-80.
- [9] Sullivan PM, Mezdoor H, Quarfordt SH, Maeda N. Type III hyperlipoproteinemia and spontaneous atherosclerosis in mice resulting from gene replacement of mouse Apoe with human Apoe*2. *J Clin Invest* 1998;102(1):130-5.
- [10] Mihovilovic M, Robinette JB, DeKroon RM, Sullivan PM, Strittmatter WJ. High-fat/highcholesterol diet promotes a S1P receptor-mediated antiapoptotic activity for VLDL. *J Lipid Res* 2007;48(4):806-15.
- [11] Huebbe P, Nebel A, Siebert S, Moehring J, Boesch-Saadatmandi C, Most E, et al. APOE epsilon4 is associated with higher vitamin D levels in targeted replacement mice and humans. *FASEB J* 2011;25(9):3262-70.
- [12] Mathes WF, Kelly SA, Pomp D. Advances in comparative genetics: influence of genetics on obesity. *Br J Nutr* 2011;106(Suppl. 1):S1-10.
- [13] Lokki AI, Jarvela I, Israelsson E, Maiga B, Troye-Blomberg M, Dolo A, et al. Lactase persistence genotypes and malaria susceptibility in Fulani of Mali. *Malar J* 2011;10:9.
- [14] Mulcare CA, Weale ME, Jones AL, Connell B, Zeitlyn D, Tarekegn A, et al. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. *Am J Hum Genet* 2004;74(6):1102-10.
- [15] Gallego Romero I, Basu Mallick C, Liebert A, Crivellaro F, Chaubey G, Itan Y, et al. Herders of Indian and European Cattle Share Their Predominant Allele for Lactase Persistence. *Mol Biol Evol* 2012 Jan;29(1):249-60.

- [16] Hannelius U, Gherman L, Makela VV, Lindstedt A, Zucchelli M, Lagerberg C, et al. Large-scale zygosity testing using single nucleotide polymorphisms. *Twin Res Hum Genet* 2007;10(4):604-25.
- [17] Wood AC, Neale MC. Twin studies and their implications for molecular genetic studies: endophenotypes integrate quantitative and molecular genetics in ADHD research. *J Am Acad Child Adolesc Psychiatry* 2010;49(9):874-83.
- [18] Llewellyn CH, van Jaarsveld CH, Boniface D, Carnell S, Wardle J. Eating rate is a heritable phenotype related to weight in children. *Am J Clin Nutr* 2008;88(6):1560-6.
- [19] Malamos B, Koutras DA, Kostamis P, Rigopoulos GA, Zerefos NS, Yataganas XA. Endemic goitre in Greece: a study of 379 twin pairs. *J Med Genet* 1967;4(1):16e18.
- [20] Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, Wagenknecht LE, et al. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans. *J Clin Endocrinol Metab* 2008;93(9):3381-8.
- [21] Hazra A, Kraft P, Lazarus R, Chen C, Chanock SJ, Jacques P, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. *Hum Mol Genet* 2009;18(23):4677-87.
- [22] Mendoza Torres E, Varela Prieto LL, Villarreal Camacho JL, Villanueva Torregroza DA. Diagnosis of adult-type hypolactasia/lactase persistence: genotyping of single nucleotide polymorphism (SNP C/T-13910) is not consistent with breath test in Colombian Caribbean population. *Archivos de Gastroenterologia* 2012;49(1):5-8.
- [23] Moleres A, Ochoa MC, Rendo-Urteaga T, Martinez-Gonzalez MA, Azcona San Julian MC, Martinez JA, et al. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children. *Br J Nutr* 2011:1-6.
- [24] Katan MB. Commentary: Mendelian Randomization, 18 years on. *Int J Epidemiol* 2004;33(1):10-1.
- [25] Trompet S, Jukema JW, Katan MB, Blauw GJ, Sattar N, Buckley B, et al. Apolipoprotein e genotype, plasma cholesterol, and cancer: a Mendelian randomization study. *Am J Epidemiol* 2009;170(11):1415-21.
- [26] Burgess S, Thompson SG. Bias in causal estimates from Mendelian randomization studies with weak instruments. *Stat Med* 2011;30(11):1312-23.
- [27] Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer* 2011;11(12):886-95.
- [28] McLaren CE, Garner CP, Constantine CC, McLachlan S, Vulpe CD, Snively BM, et al. Genomewide association study identifies genetic loci associated with iron deficiency. *PLoS One* 2011;6(3):-17390.
- [29] Shaheen NJ, Silverman LM, Keku T, Lawrence LB, Rohlfes EM, Martin CF, et al. Association between hemochromatosis (HFE) gene mutation carrier status and the risk of colon cancer. *J Natl Cancer Inst* 2003;95(2):154-9.
- [30] Chan AT, Ma J, Tranah GJ, Giovannucci EL, Rifai N, Hunter DJ, et al. Hemochromatosis gene mutations, body iron stores, dietary iron, and risk of colorectal adenoma in women. *J Natl Cancer Inst* 2005;97(12):917-26.
- [31] Higuchi S, Matsushita S, Muramatsu T, Murayama M, Hayashida M. Alcohol and aldehyde dehydrogenase genotypes and drinking behavior in Japanese. *Alcohol Clin Exp Res* 1996;20(3):493-7.
- [32] Oze I, Matsuo K, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Alcohol drinking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2011;41(5):677-92.
- [33] Corella D, Tai ES, Sorli JV, Chew SK, Coltell O, Sotos-Prieto M, et al. Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene-saturated fat interaction. *Int J Obes (Lond)* 2011;35(5):666-75.
- [34] Garaulet M, Corbalan MD, Madrid JA, Morales E, Baraza JC, Lee YC, et al. CLOCK gene is

- implicated in weight reduction in obese patients participating in a dietary programme based on the Mediterranean diet. *Int J Obes (Lond)* 2010;34(3):516-23.
- [35] Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, Tsai MY, et al. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am J Clin Nutr* 2009;90(6):1466-75.
- [36] Corella D, Arnett DK, Tucker KL, Kabagambe EK, Tsai M, Parnell LD, et al. A High Intake of Saturated Fatty Acids Strengthens the Association between the Fat Mass and Obesity-Associated Gene and BMI. *J Nutr* 2011;141(12):2219-25.
- [37] Phillips CM, Goumidi L, Bertrais S, Field MR, Peloso GM, Shen J, et al. Dietary saturated fat modulates the association between STAT3 polymorphisms and abdominal obesity in adults. *J Nutr* 2009;139(11):2011-17.
- [38] Ashfield-Watt PA, Pullin CH, Whiting JM, Clark ZE, Moat SJ, Newcombe RG, et al. Methylene-tetrahydrofolate reductase 677C>T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: a randomized controlled trial. *Am J Clin Nutr* 2002;76(1):180-6.
- [39] Sarkkinen E, Korhonen M, Erkkilä A, Ebeling T, Uusitupa M. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *Am J Clin Nutr* 1998;68(6):1215-22.
- [40] Kuhn TS. *The structure of scientific revolutions*. 3rd ed. Chicago, IL: University of Chicago Press; 1996.
- [41] Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005;2(8):e124.
- [42] Ioannidis JP. Why most discovered true associations are inflated. *Epidemiology* 2008;19(5):640-8.
- [43] Ioannidis JP, Trikalinos TA. Early extreme contradictory estimates may appear in published research: the Proteus phenomenon in molecular genetics research and randomized trials. *J Clin Epidemiol* 2005;58(6):543-9.
- [44] Willig AL, Casazza KR, Divers J, Bigham AW, Gower BA, Hunter GR, et al. Uncoupling protein 2 Ala55Val polymorphism is associated with a higher acute insulin response to glucose. *Metabolism: clinical and experimental* 2009;58(6):877-81.
- [45] Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *J Nutrigenetics Nutrigenomics* 2011;4(2):69-89.
- [46] Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. *Genet Med* 2002;4(2):45-61.

BÖLÜM 7

Nutrigenetiğin Pratik Kullanımları

TERİMLER

- DRI: Diyet Referans Alımları, sağlıklı insanlar için alım önerilerini özetler.
- EAR: Tahmini Ortalama Gerekşinim, grupların yeterliliğinin değerlendirilmesi için kullanılan alım düzeyidir.
- Çok modlu dağılım: Farklı ortalamaları olan alt grupların oluşturduğu normal olmayan dağılımdır.
- RDA: Önerilen Diyet Alımı, çoğu insanın ihtiyaçlarını karşılayan alım seviyesidir.

ÖZET

Nutrigenetik bilim ve uygulamanın birçok farklı kullanımı vardır. En çok önemli olan kavramları ise beslenmeye bireysel duyarlılığı düşündürmekte ve bu konseptlerle benzerlik göstermektedir. Nutrigenetik testler; beklenen sağlık yararı, gerekli performans, laboratuvar analizleri ve maliyetleri hesaba katılarak dikkatli bir şekilde seçilmelidir. Etik kaygılar genellikle özerklik ve gizlilik ile ilgilidir. Hastalar ve danışanlar başta kendilerini içine aldıkları durumu anlamalıdır. Tüm genetik testler açık ve net bir şekilde belgelenmiş onam bilgisi içermeli ve bireylerin rızasını gerektirmektedir. Sağlık hizmeti sunucularının, genetik analizlerin yanlış sonuçlar verebileceğini bilmesi gerekmektedir. Diğer laboratuvar testleri kadar sık olmasa da sonuçların yorumlanması yeni araştırmalarla birlikte değişebilmektedir.

Kişiselleştirilmiş beslenmenin pratik uygulamasına ilgi artmaya devam etmektedir. Genel tüketiciler, derinlemesine rehberlik olmadan beslenme profillerini değiştirememektedir. Bu durum, bireyselleştirilmiş metin mesajları veya daha kapsamlı bilgisayar tabanlı beslenme rehberliği ile yapılabilmektedir.

Popülasyon çapında kılavuzların ve tüm düzeylerdeki beslenme araştırmalarının geliştirilmesi için, bireylerin farklı beslenme ihtiyaçlarının daha iyi anlaşılması gerekmektedir. Artık çoğu insanın belirli bir beslenme faktörüne az ya da çok aynı şekilde yanıt verdiği varsayımı kabul görmemektedir. Beslenme kılavuzlarının geliştirilmesinde yeni analitik

KAYNAKLAR

- [1] Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone JD. Good laboratory practices for molecular genetic testing for heritable diseases and conditions. *MMWR* 2009;58(RR-6):1-37.
- [2] Hofgartner WT, Tait JF. Frequency of problems during clinical molecular-genetic testing. *Am J Clin Pathol* 1999;112(1):14-21.
- [3] Mahadevan MS, Benson PV. Factor V null mutation affecting the Roche LightCycler factor V Leiden assay. *Clin Chem* 2005;51(8):1533-5.
- [4] Imai K, Kricka LJ, Fortina P. Concordance study of 3 direct-to-consumer genetic-testing services. *Clin Chem* 2011;57(3):518-21.
- [5] Plebani M. The detection and prevention of errors in laboratory medicine. *Ann Clin Biochem* 2010;47(Pt 2):101-10.
- [6] Ramsden SC, Deans Z, Robinson DO, Mountford R, Sistermans EA, Grody WW, et al. Monitoring standards for molecular genetic testing in the United Kingdom, the Netherlands, and Ireland. *Genet Test* 2006;10(3):147-56.
- [7] Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. Total mortality by transferrin saturation levels: two general population studies and a metaanalysis. *Clin Chem* 2011;57(3):459-66.
- [8] Kurppa K, Rasanen T, Collin P, Iltanen S, Huhtala H, Ashorn M, et al. Endomysial antibodies predict celiac disease irrespective of the titers or clinical presentation. *World J Gastroenterol* 2012;18(20):2511-6.
- [9] Riddle MS, Murray JA, Porter CK. The incidence and risk of celiac disease in a healthy US adult population. *Am J Gastroenterol* 2012;107(8):1248-55.
- [10] Gibson PR, Shepherd SJ, Tye-Din JA. For celiac disease, diagnosis is not enough. *Clin Gastroenterol Hepatol* 2012;10(8):900-901.
- [11] Nielsen DE, El-Sohemy A. A randomized trial of genetic information for personalized nutrition. *Genes Nutr* 2012 Mar 11 [Epub ahead of print].
- [12] Kubaszek A, Pihlajamaki J, Punnonen K, Karhapaa P, Vauhkonen I, Laakso M. The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes* 2003;52(2):558-61.
- [13] Watkins WS, Rohrwasser A, Peiffer A, Leppert MF, Lalouel JM, Jorde LB. AGT genetic variation, plasma AGT, and blood pressure: An analysis of the Utah Genetic Reference Project pedigrees. *American Journal of Hypertension* 2010;23(8):917-23.
- [14] Ashfield-Watt PA, Pullin CH, Whiting JM, Clark ZE, Moat SJ, Newcombe RG, et al. Methylene-tetrahydrofolate reductase 677C>T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: a randomized controlled trial. *Am J Clin Nutr* 2002;76(1):180-6.
- [15] Xu X, Gammon MD, Wetmur JG, Rao M, Gaudet MM, Teitelbaum SL, et al. A functional 19-base pair deletion polymorphism of dihydrofolate reductase (DHFR) and risk of breast cancer in multivitamin users. *Am J Clin Nutr* 2007;85(4):1098-102.
- [16] Shen J, Gammon MD, Terry MB, Wang L, Wang Q, Zhang F, et al. Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2005;14(2):336-42.
- [17] Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, Tucker K, et al. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. *Arch Intern Med* 2009;169(20):1897-906.
- [18] Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE, et al. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007;86(3):743-51.
- [19] Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;360(8):753-64.

- [20] Zellner C, Pullinger CR, Aouizerat BE, Frost PH, Kwok PY, Malloy MJ, et al. Variations in human HM74 (GPR109B) and HM74A (GPR109A) niacin receptors. *Hum Mutat* 2005;25(1):18-21.
- [21] Soudijn W, van Wijngaarden I, Ijzerman AP. Nicotinic acid receptor subtypes and their ligands. *Medicinal Res Rev* 2007;27(3):417-33.
- [22] Owen SA, Hider SL, Martin P, Bruce IN, Barton A, Thomson W. Genetic polymorphisms in key methotrexate pathway genes are associated with response to treatment in rheumatoid arthritis patients. *Pharmacogenomics J* 2012 Mar 27 [Epub ahead of print]
- [23] Malhotra AK, Correll CU, Chowdhury NI, Muller DJ, Gregersen PK, Lee AT, et al. Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. *Arch Gen Psychiatry* 2012 May 7 [Epub ahead of print].
- [24] Zillikens MC, van Meurs JB, Sijbrands EJ, Rivadeneira F, Dehghan A, van Leeuwen JP, et al. SIRT1 genetic variation and mortality in type 2 diabetes: interaction with smoking and dietary niacin. *Free Radic Biol Med* 2009;46(6):836-41.
- [25] Bernstein IL, Longley A, Taylor EM. Amiloride sensitivity of chorda tympani response to NaCl in Fischer 344 and Wistar rats. *Am J Physiol* 1991;261(2 Pt 2):R329-33.
- [26] Hwang YW, Kim SY, Jee SH, Kim YN, Nam CM. Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies. *Nutr Cancer* 2009;61(5):598-606.
- [27] Hedelin M, Balter KA, Chang ET, Bellocco R, Klint A, Johansson JE, et al. Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006;66(14):1512-20.
- [28] Akaza H. Prostate cancer chemoprevention by soy isoflavones: Role of intestinal bacteria as the "second human genome." *Cancer Sci* 2012;103(6):969-75.