The Genetics of Obesity in Transition

Ellen W. Demerath

University of Minnesota, School of Public Health, Division of Epidemiology and Community Health, Minneapolis, USA

A B S T R A C T

Recent advances in human genetics have revealed a number of genes influencing the susceptibility to obesity and related conditions, but it is likely that their contribution to disease is contingent on numerous environmental factors. As the obesity epidemic has occurred over a relatively short period of recent history, use of gene-by-year of birth analysis may be a useful approach for quantifying, in aggregate, the interaction between genetic susceptibility to obesity and the numerous known and unknown environmental factors that have changed during nutrition and health transitions globally during this recent increase in obesity rates. Evidence from one family-based longitudinal study set in the United States is showcased, which points to significant increases in the effect of common genetic variants on childhood and adulthood BMI over an 80 year period spanning from 1929 to the present. First, common genetic variants previously known to be associated with age at menarche through genome-wide association analysis were examined in aggregate using a genetic risk score approach. The menarche genetic risk score, composed of 42 single-nucleotide polymorphisms (SNPs) was significantly associated with peri-pubertal BMI in both boys and girls, but the magnitude of the association was strongly dependent on year of birth, with greater effect as birth year increased. Second, a similar approach was taken using instead a BMI genetic risk score composed of 32 common variants previously found to be associated with BMI. This score was strongly associated with adulthood BMI, waist circumference, and skinfold thickness, as expected, but the magnitude of the association increased with later year of birth. Such gene-environment interactions call for greater focus on the mechanisms by which environmental factors impact the functional output of the human genome, including how epigenetic mechanisms may be altered during social, technological, nutritional, and ecological transitions.

Key words: *obesity, genetics, gene-by-environment interaction, nutrition transition, epigenetics, longitudinal, lifecourse*

Introduction

Obesity prevalence has increased dramatically over the past 30 years to 17% of children and 35% of adults in the United States[1]; 1.7 billion people around the globe are overweight and 310 million are obese with rates of obesity tripling in the last 20 years in poorer countries. The greatest increases are now in the Middle East, China, Southeast Asia, and the Pacific islands nations. It is forecasted that Type 2 Diabetes Mellitus will increase 170% in poorer countries and by 41% in industrialized countries in the next 20 years[2]. The transitions in human nutrition that have driven the increased prevalence of these diseases are primarily technological in origin. Mass food production has lead to the lower cost of simple sugars and fats and increased average caloric intakes. The widespread use of automobiles for transportation and reduction in need for manual labor and screen-based entertainment has lowered energy expenditure. Clearly, the nutritional and lifestyle transition we are witnessing is not uniform, and there are vast disparities within and between countries in the rates of undernutrition, infectious disease, and mortality; transitions are complex. Nonetheless, because of the massive effect of recent environmental changes on obesity and health, it might be assumed that the genetic contribution to human variation is minor and that differences between individuals are only due to lifestyle factors. After all, allelic frequencies have not changed within populations over the recent period of the obesity epidemic. It is the environment in which those alleles function that has changed. One might reasonably question whether genetic variation could have any major role in the current picture of obesity.

Human Genetics Research in Transition

The field of human genetics has undergone a transition in parallel with the obesity epidemic. Until 1990, vir-

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tually all human genetic studies were either quantitative (i.e., looking at similarities within and between relatives to determine the overall genetic influence), were tracking high penetrance variants through families to identify single gene disorders, or were focused on a small number of polymorphisms in small numbers of study subjects. The latter approach, of selecting a small number of variants in a small number of genes and studying them in a small number of individuals, essentially did not work for the multifactorial diseases of greatest public health significance, and which have been the outcome of health transitions worldwide. Numerous genes on every chromosome were reported to be associated with obesity, but most of these associations were false positives; they were not replicated in any other studies. Therefore, there was relatively little insight into the genetic regulation of appetite, satiety, taste, proclivity to exercise, metabolic rate, and lipid and carbohydrate trafficking in humans. Since then, an explosion in high-throughput molecular techniques has reduced the costs of genotyping and gene expression studies, so that millions of variants can be tested in one experiment in large numbers of subjects. At the same time, massive advances in computer processing speed and complexity and reduction in costs have allowed geneticists to map and deeply scrutinize human genomic variation. Statistical genetics became far more sophisticated. Finally, data sharing across institutions and studies has increased the number of subjects that can be tested at once. Whereas a very large genetic study of obesity in 1990 might have included 2,000 individuals, recent work includes up to a million subjects through collaboration of hundreds of scientists.

Genetics of Obesity and other Chronic Diseases in 2012

What is the result of this epidemic of super-sized genetic research? Using genome-wide association approaches, in which 500,000 to 1 million genetic variants are examined for association with disease traits or risk factors in tens or hundreds of thousands of human subjects, collaborative efforts have identified approximately 32 variants contributing to BMI and obesity[3] and 53 influencing glycemic control and diabetes[4]. Growth and development traits have been examined as well – 42 variants contributing to age at menarche[5] and over 180 different, independent variants contribute to normal variation in human stature. The good news is that many novel gene pathways have been identified, which is the first step toward effective pharmaceutical development and also an important starting place for epidemiology – we are finally beginning to quantify population-level genetic risks for disease. In the case of BMI and obesity, for instance, many of the genes identified are neurotrophic factors in pathways involved in the central regulation of appetite and energy expenditure, while fewer are involved in lipid metabolism. In addition, there are certain regions of the genome that are now known to be enriched for age-associated diseases of transition and reduced longevity (cancer, diabetes, obesity, cardiovascular disease)[6], while most of the genome harbors relatively little chronic-disease related variation.

However, genome-wide association studies are also somewhat disappointing in that the phenotypic variance explained by these common polymorphisms is low. Family studies repeatedly show that about 50% of the variation in BMI is due to genetic effects, but the 32 well-replicated BMI and obesity SNPs mentioned above account for less than 3% of BMI variation and the 180 height SNPs account for about 10% of human height variation. This is the so-called »missing heritability« problem, and may suggest that indeed, genetic variation plays a fairly minor role in distinguishing individual differences in health-related traits. However, there is also the possibility that we are looking in the wrong place for relevant genetic variants[7]. For example, the field of genetic epidemiology was largely influenced by the »common-disease--common variant« theory, in which common diseases were thought to be influenced by a set of common (minor allele frequency >5%) variants, and therefore existing genome-wide arrays only target these common variants. Rarer variants with larger effect sizes may contribute greater variance to obesity and other such common disease traits. Other possibilities are that there are structural variants such as copy number variants that are not picked up by existing arrays, and that genetic variants do not work in isolation but in large networks and so multiple gene-gene interactions must be assessed. It is also possible that heritability estimates are inflated by shared environment between relatives. Indeed confounding by familial environment has been a frequent criticism leveled at genetic studies of normal human variation, and except for studies of twins reared apart, it is true that there is little way to segregate environmental and genetic factors in family studies. However, genome-wide marker data are being used to empirically estimate the genetic and phenotypic covariance among relatives, which is not inflated by shared environment as is the kinship coefficient. Thus far, these estimates appear to be very similar to traditional heritability estimates[8].

Gene-by-Environment Interaction in Obesity

Another possibility is that to date, environmental heterogeneity within and between studies have not been effectively addressed in large-scale genetic studies, which have focused first on testing the main effects of genetic variants. Could taking account of environmental heterogeneity improve our understanding of the contribution of genetic factors to growth and obesity traits? To date, the best example of gene-by-environment interaction on adiposity is the interaction of physical activity (PA) level with the »fat mass and obesity linked« gene, FTO, discovered via genome-wide association study in 2007[9] and the strongest genetic susceptibility locus for obesity yet discovered. With numerous receptors in the arcuate nucleus of the hypothalamus, FTO functions to regulate appetite

and energy expenditure[10]. SNPs found within intron 1 of FTO are associated with BMI and body fatness across numerous populations[11], and in both children and adults. However, the association of FTO variants on adiposity depends on physical activity level, with stronger associations in individuals with lower PA level. A meta-analysis of over 200,000 individuals confirmed this interaction in numerous populations[12], where each copy of the risk allele increased the risk of obesity by 30% in low PA individuals, but by only 20% in high PA individuals. We found no interaction effect in children.

This finding has large public health implications, as it is a proof of principle that increased physical activity, a core strategy for chronic disease prevention, has the potential to counteract the effects of a putatively deleterious genotype on obesity. However, the meta-analysis interaction effect was nonetheless fairly small and the study was predominantly restricted to European ancestry individuals. We recently looked at this question in approximately 3,000 African Americans (AA) and 7,000 European Americans (EA) in the Atherosclerosis Risk in Communities (ARIC) study[13]. PA was coded as a dichotomous variable (lowest tertile versus middle or highest tertile) of sports activity. In race- and sex-stratified models, we found no interaction effect in either AA or EA women, but found a strong interaction of FTO SNP rs9939609 by low PA on BMI in both AA men (P=0.001) and EA men (P=0.036). The interaction of rs9939609 × PA was also significant for WC (P=0.0016 in AA men and P=0.029 in EA men) and for SKF (P=0.0005 in AA men and P=0.012 in EA men). As shown in Figure 1, the SNP had a stronger association with adiposity traits in men with low PA than in men with high PA. In AA men in particular, the additive per allele effect of the SNP was nearly 10 times greater in those with low PA than in those with high PA, and the SNP had no significant in those with moderate or high sports activity. This suggests that environmental variation may mask genetic effects when those differences are not accounted for.

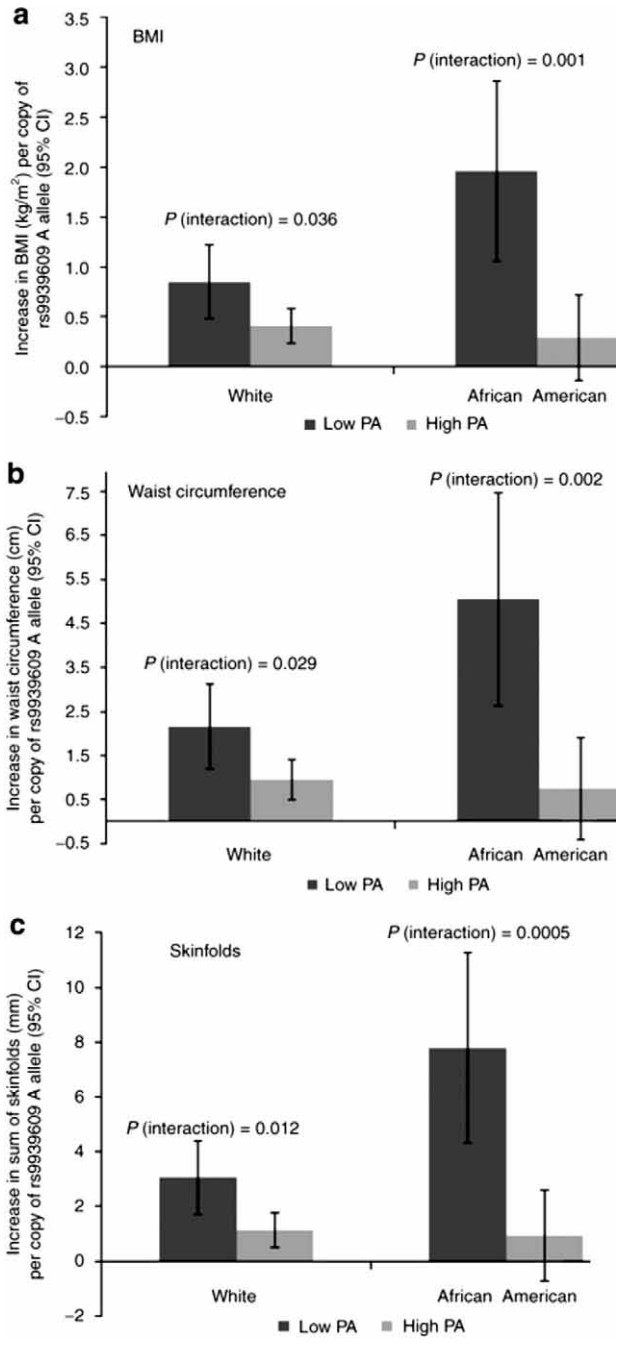

Fig. 1. Interaction between FTO genotype (rs9939609) and physical activity level (PA) on BMI, Waist Circumference, and sum of skinfolds in African American and European American men (from Demerath et al., 2011).

Gene-by-Year of Birth as a Type of Gene-by-Environment Interaction

The results above are for a single variant in interaction with a single environmental factor. While methods of genome-wide interrogation of gene-environment interaction are ongoing, nonetheless, no single study or group of studies will have high quality data on all possible exposures and thus it will be exceedingly difficult to conduct meta-analysis that will be able to accurately capture the totality of gene-by-environment effects on a trait. One approach would be to take advantage of the *known changes over time* in numerous aspects of nutrition and energetic during the obesity epidemic. In other words, with genetic data on individuals from the same genetically stable population tracked over time, one could test the hypothesis of gene-by-secular trend interaction. After adjusting for age effects, the degree to which the genetic association of genes with adiposity varies with year of birth would be a measure of global gene-by-environment interaction. This idea is supported by the fact that as the obesity epidemic has continued, increases in BMI have been seen more at the upper tails of the distribution than in the mean. For example, in children, there was no increase in median BMI from 1999 to 2008 except that an increase occurred in boys aged 6-19 years above the 97th percentile. In adults, this is even clearer; the

prevalence of adults with BMI > 50 increased 9-fold between 1985 and 2005, while the prevalence of adults with BMI > 30 approximately doubled[14]. Ravussin and Bouchard have presented a helpful conceptual model of this phenomenon[15], and illustrated in Figure 2. Genetic susceptibility to obesity can be defined as a variable resulting from allelic variations at a set of obesity genes in low-risk (restrictive, left distribution) and high-risk (obesigenic, right distribution) environments. In a »restrictive« environment in which caloric availability is limited and physical activity is high, individuals with a low genetic susceptibility (Obesity Resistant, OR) will have a very low body mass index and those with a high genetic susceptibility (Obesity Prone, OP) will have a higher BMI (higher degree of adiposity). Yet, even those who were obesity prone will have relatively low BMI compared to the BMI distribution in an »obesigenic« environment. When these obesity prone individuals move into an environment replete with high fat foods and low demand for physical activity, the overall distribution of adiposity will shift to the right. The same scenario is represented in the lower panel, showing the presence of a gene × environment interaction in which the »obesigenic« environment amplifies the effects of genetic susceptibility in obesity prone individuals compared to obesity resistant individuals.

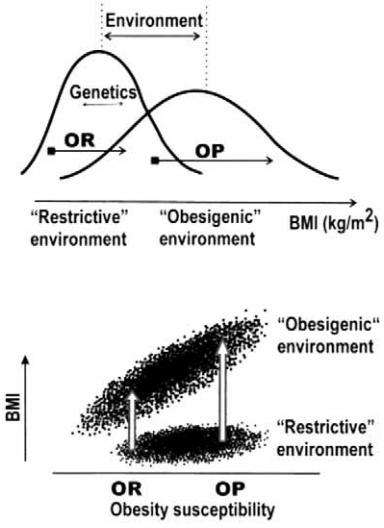

Fig. 2. Hypothesized differences in the phenotypic impact of the genetic susceptibility to obesity under obesogenic and restrictive environments (from Ravussin & Bouchard, 2000).

Gene-by-Year of Birth Interaction Effects on Childhood and Adulthood BMI in the Fels Longitudinal Study

The Fels Longitudinal Study includes approximately 1,400 non-Hispanic white subjects born in southwestern OH and was initiated in 1929 to track individuals from birth to adulthood for measurement of normative growth and cardiovascular disease risk factor development. The Fels Longitudinal Study is a family study, which is now following a 4th generation of subjects, and has both genome-wide genotype data and information on BMI and adiposity traits over the life course in individuals born from 1929 to the present. This permits examination of how genetic influences on these traits have changed over time. Like the surrounding society, child and adulthood growth and BMI have changed during this period, mirroring trends in nutrition in the wider society. For instance, birth weight has increased with increasing maternal BMI[16], and now this has lead to a higher, later age at peak infant BMI (Johnson et al., personal communication). Childhood BMI patterns have shifted toward earlier adiposity rebound and faster adolescent BMI gains[17], and age at menarche in girls has declined in the last two decades from a mean of 12.8 years in girls born between the 1930's – 1960's to a mean of 12.3 years in girls born in the 1980's[18]. In turn, adulthood BMI has increased over the same period[18].

In two recent studies, we have shown that the magnitude of these increasing trends in adiposity depend on genotype((Johnson et al., in press); (E. W. Demerath et al., in press). First, we calculated a genetic risk score for early menarche using the 42 well-replicated SNPs reported by Elks et al.[5], and a genetic risk score for higher BMI using the 32 SNPs reported by Speliotes et al., 2010. That is, for each individual in the study, we counted the number of alleles for each of these SNPs that was associated with earlier menarche, and higher BMI, respectively. We then used maximum likelihood-based variance components analysis to estimate trait heritabilities, main effects of the genetic risk score (using a 1 df test) and year of birth (YOB), and the genetic risk score-by-YOB interaction, as well as other covariates.

In the first case, we tested whether the menarche genetic risk score was associated with childhood BMI Z score (WHO standard) in over 500 boys and girls seen longitudinally during the peripubertal period, from 6 years prior to peak height velocity to 6 years after peak height velocity, and whether there was a menarche genetic risk score x YOB interaction at each of those ages. A representative subset of the results are shown in Figure 3. These results examine a more conservative risk score composed of only 29 SNPs, with deletion of 14 SNPs already documented to be associated with BMI. Interestingly, there were significant main effects of the genetic risk score on BMI Z score in both sexes, which suggests that the menarche variants are related to general growth and development seen in both sexes and not ovarian development only. Second, the genetic risk score had a positive interaction with year of birth, such that the increase in BMI Z score per allele increase in the genetic risk score increased across subsequent decades of birth; this was true for both pre-pubertal BMI (4 years prior to peak height velocity) and post-pubertal BMI (4 years after peak height velocity). We know of no other studies that have documented such a gene-by-time interaction for childhood BMI, but the results lend support to the no-

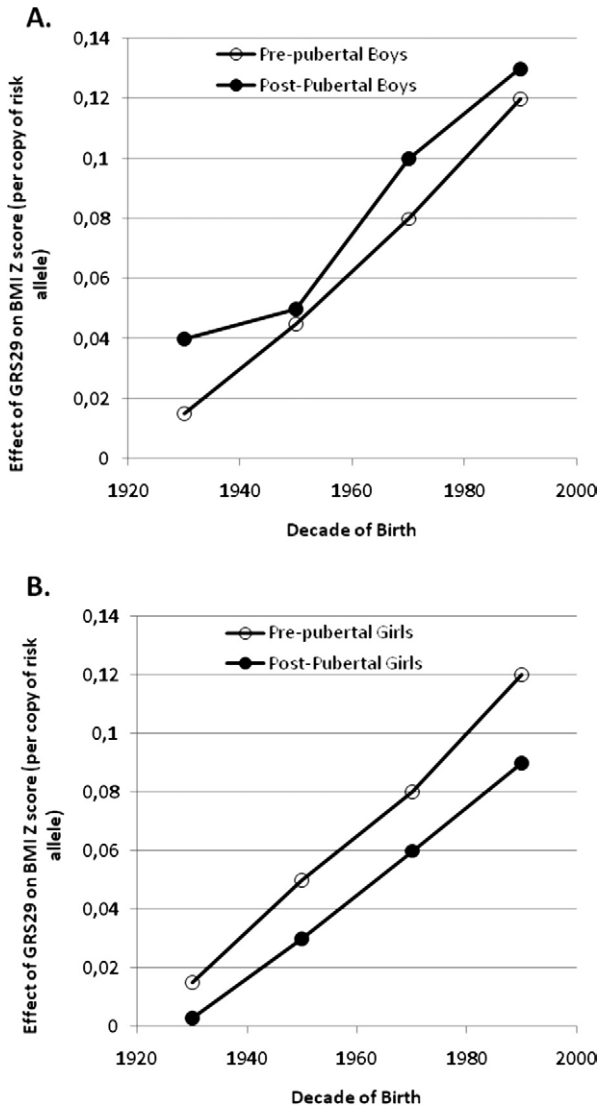

Fig. 3. Estimates effects of an early menarche genetic risk score on pre-pubertal BMI (4 years prior to peak height velocity) and post-pubertal BMI(4 years after peak height velocity in boys and girls born in 1930, 1950, 1970, and 1990 (data from Johnson et al., in press).

tion, hypothesized by Ravussin and Bouchard[15], among others, that the epidemic of obesity seen in the past 30 years is at least partially due to alteration in the influence of genes over time though increases in caloric intake and lower energy expenditure. The Fels Longitudinal Study unfortunately does not have data on caloric intake and physical activity collected systematically over the entire period of the study, making specific behavioral contributors to the interaction difficult or impossible to pinpoint. Nonetheless, our strategy here is to utilize birth year as a proxy for numerous unmeasured environmental factors affecting energetics and nutrition over this period of time, and our data support the hypothesis of a change in the influence of developmental timing genes on childhood BMI.

In the second case[20], we tested whether a BMI genetic risk score was differentially associated with BMI, waist circumference (WC), sum of four skinfolds, and other anthropometric measures of adiposity in 907 adults (measured at 20–60 years of age) born at different points in time. As expected, significant positive main effects were observed for both the obesity genetic risk score and for YOB for most traits; in addition, significant positive GRS-by-YOB effects were found for BMI ($p=0.0001$), WC ($p=0.0001$), and SKF ($p=0.0001$). For each 1 allele increase in the genetic risk score, we found an estimated increase of 0.5 mm in the sum of skinfolds among individuals born in 1930 compared with an estimated 3 mm increase among individuals born in 1980. Likewise, the effect of 1 allele increase on BMI was 0.15 kg/m^2 in individuals born in 1930 and 0.55 kg/m^2 in individuals born in 1980. It is true that there are likely many other additive genetic variants contributing to adulthood BMI, as evidenced by significant heritability even after adjusting for the genetic risk score and its interactions with YOB. Nonetheless, these novel findings support the hypothesis that the influence of common obesity susceptibility variants has increased over the 20th century. Data from Swedish conscripts also shows that the heritability of BMI, that is, its genetic variance, has increased over the same period[21]. Again, these data suggest that although environmental factors are primary in driving the obesity epidemic, the changing environment has altered the action of genes. Furthermore, it suggests that if anything, genetic variants involved in human adiposity have not declined in influence with nutritional transition, but rather that their full range of expression may only be reached with the evolutionarily extreme exposures to obesogenic environments that we now see.

Epigenetic Modification in Gene-by-Year of Birth Interactions on Obesity Traits

One possible mechanism that explains how gene action can change with changing environmental conditions is epigenetic modification. Whereas the individual genetic sequence (base pair sequence) is fixed at gamete formation and is identical in all cells regardless of cell type, genetic expression varies greatly over the course of embryogenesis, fetal development, childhood growth, and aging and varies by cell type. Epigenetics is the study of chemical changes to the DNA molecule affecting its conformational structure (euchromatin or chromatin) and ultimately the transcriptional read-out of the genome. Addition or subtraction of methyl (CH_3) groups to cytosine residues (DNA methylation) and modification of the histone bodies around which DNA is coiled (histone modification) are two processes that change the conformational structure of DNA. Both DNA methylation and histone modification, among other epigenetic changes, affect the ability of the transcriptional machinery of the cell to access a particular segment of the DNA. For example, DNA methylation events tend to cluster in areas of the genome having numerous CG repeats (called CpG is-

lands), which are often upstream of the promoter region of genes. This decreases the ability of transcription factors to bind to the promoter region to initiate transcription.

As mentioned above, the epigenetic state of the genome changes with age; DNA goes through large fluctuations in global demethylation and remethylation during embryogenesis[22], and tends to becomes more hypomethylated with increasing age[23]. Epigenetic marks are also modifiable by environmental factors such as the nutrient content of the diet[24], maternal behavior and stress[25], and environmental pollutants[22].

At this point, few large human studies of differential DNA methylation have been conducted, and the environmental determinants of histone modification are even less explored. However, it is possible that typical patterns of epigenetic regulation of gene expression in humans are being altered by shifts in the human environment, and may be partly responsible for the gene-by-year of birth interactions on obesity we reported above. A recent study found that exposure to a high-fat diet was not only associated with peripheral insulin resistance, but also influenced DNA methylation of the peroxisome proliferator-activated receptor gamma, coactivator 1-alpha (PPARGC1A) gene in skeletal muscle[27], and a recent study found differential DNA methylation in obese and normal weight preadolescents at 20 different loci[28]. However, none of these loci included FTO or other known obesity loci. Rather, it may be that genetic variation that influences obesity does so by altering epigenetic marks in neighboring or distant regions of the genome. For example, individuals carrying FTO risk alleles have differential methylation of other genes[28], and greater methylation of sites within Intron 1 of the FTO gene itself. Complex interactions between genetic susceptibility to obesity (sequence variation), epigenetic changes in and around obesity genes, and environmental factors are likely operating. This is a very fertile area for future research, and studies are needed to understand the extent to which human epigenetic variation is changing during social and environmental transition. Such work is particularly important in regions of the world where environmental change is occurring rapidly.

Conclusion

In summary, this essay argues that genes play a major role in the susceptibility to obesity, but that to further the field, greater attention must be paid to gene-environment interaction. Particular emphasis should be placed on documenting how epigenetic mechanisms may be altered during social, technological, nutritional, and ecological transitions. Evidence from one family-based longitudinal study set in the United States is showcased, which points to significant increases in the effect of common genetic variants on BMI over an 80 year period spanning from 1929 to the present.

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E. W. Demerath

University of Minnesota, School of Public Health, Division of Epidemiology and Community Health, 1300 2nd Street S, Minneapolis, MN 55455 USA
e-mail: ewd@umn.edu

GENETIKA PRETILOSTI U TRANZICIJI

S A Ž E T A K

Recentni napreci u humanoj genetici otkrili su veliki broj gena odgovornih za sklonost pretilosti i srodnim stanjima, no oni su najvjerojatnije u uskoj vezi i s brojnim okolišnim utjecajima. S obzirom na brzi razvoj epidemije pretilosti u posljednje vrijeme, analize koje mogu kvantificirati interakciju genetičke predispozicije za pretilost i brojnih poznatih i još nepoznatih okolišnih faktora koji su se javili sa prehrambenom i zdravstvenom tranzicijom pokazale su se vrlo korisnima. Dokaz su pružile longitudinalne studije provedene na obiteljima u SAD-u u razdoblju od 80 godina (od 1929. do danas), koje upućuju na značajan porast utjecaja uobičajenih genskih varijanti na indeks tjelesne mase djece i odraslih. Istraživane su uobičajene genske varijante za koje su asocijacijske studije koje obuhvaćaju cijeli genom pokazale da su povezane s dobi menarhe i to koristeći više genetičkih markera s ciljem otkrivanja stupnja rizika. Pokazalo se da je genetički marker rizika za dob nastupanja menarhe, koji se sastoji od 42 polimorfizma jednog nukleotida, značajno povezan s pubertetskim indeksom tjelesne mase i kod dječaka i kod djevojčica, no i da stupanj povezanosti znatno ovisi o godini rođenja pojedinca te da se povezanost povećava s povećanjem godine rođenja. Također, isti je pristup korišten i sa genetičkim markerom rizika za indeks tjelesne mase, koji se sastoji od 32 uobičajene genske varijante, a za koji je utvrđena povezanost sa mjerenim indeksom tjelesne mase. Očekivano, utvrđen je visok stupanj njegove povezanosti s indeksom tjelesne mase odraslih osoba, opsegom struka i debljinom kožnih nabora, no stupanj povezanosti je bio tri puta veći kod pojedinaca rođenih 1980., nego kod onih rođenih 1930. godine. Takva interakcija gena i okoliša upućuje na veliku važnost mehanizama putem kojih okolišni čimbenici utječu na funkcionalnost ljudskog genoma te nam govori kako se epigenetički mehanizmi mogu mijenjati tijekom društvenih, tehnoloških, prehrambenih i ekoloških tranzicija.