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REVIEW

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The *thrifty-genotype* hypothesis and its implications for the study of complex genetic disorders in man

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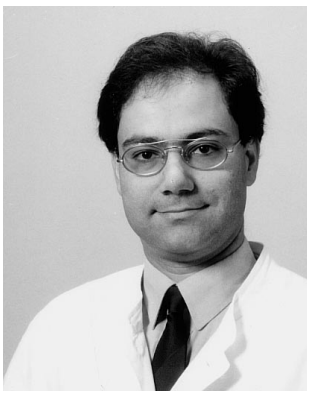
Abstract According to the "thrifty-genotype" hypothesis proposed by Neel, diseases of civilization such as non-insulin-dependent diabetes mellitus and hypertension result from a discordance between certain features of our present-day environment and our genetic make-up which evolved to fit the life of Paleolithic humans. This concept implies that while "affected" individuals harbor the "original" ancestral version of the relevant genes, healthy or "unaffected" individuals have picked up recent mutations leading to a "loss of thriftiness" of these genes. Support for this concept now comes from recent studies of the angiotensinogen gene, where an ancestral variant of the gene (*AGT* 235T), also present in primates, has now been associated with hypertension whereas a neomorphic variant (*AGT* 235M) apparently reduces the risk of high blood pressure. The implications of these findings for our understanding and approach to the study of complex genetic diseases is discussed.

Key words Genetics · Complex disease · Human evolution · Primates · Thrifty-genotype · Hypertension · Angiotensinogen · Diabetes mellitus



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Abbreviations *NIDDM* Non-insulin dependent diabetes mellitus

Introduction

The idea that common complex genetic diseases of "civilization" including obesity, hypertension, and non-insulin-dependent diabetes (NIDDM) result from the exposure of a thrifty genotype to a prodigal environment was proposed almost 35 years ago by Neel [1]. According to this concept, diseases of civilization result from a discordance between certain features of our present-day environment and our genetic make-up which evolved over time to fit the life of Paleolithic humans. Thus, individuals who are genetically predisposed to low metabolic rates, sodium conservation, and rapid mobilization of insulin in response to a carbohydrate challenge would be genetically predisposed to obesity, salt-sensitive hypertension, and NIDDM when faced with a sedentary lifestyle and a high-salt energy-dense diet.

This predisposition is clearly accentuated by the dramatic increase in life expectancy over the past two centuries in many parts of the world. In many developing countries this increase in life expectancy has occurred during the span of a few generations and is currently contributing substantially to the epidemic rise in morbidity and mortality attributable to noncommunicable disease [2]. Thus, enhanced human survival has unmasked the latent genetic susceptibility to pathological conditions that increase with age. This has been described as "Dobzhansky's limit," which states that evolution prepares us to only reach sexual maturity, and predicts that optimal well-being persists through the reproductively active years – but not much longer [3].

Clearly the cultural changes that have occurred over the past 10,000 years have far outpaced any possible genetic adaptations, especially since much of this cultural change has occurred only subsequent to the industrial revolution 200 years ago [4]. Even today periodic variability in the availability of staple nutrients and the com-

position of the diet with regard to caloric, carbohydrate, protein, and fat intake in many nonindustrialized populations remains remarkably similar to that of present-day primates, whose diet in most cases consists of a variety of plant foods but also includes occasional insects, small vertebrates, and other sources of animal protein [5]. In contrast, the contemporary diet in most industrialized countries is characterized by a markedly higher fat and sodium but lower protein, potassium, calcium, and fiber content [6]. Similarly, physical activity, which is high in free-living primates, is clearly lower in more affluent industrialized societies. Substantial epidemiological data suggest that the epidemic spread of obesity, hypertension, and NIDDM accompanying the rising affluence of populations in many parts of the developing world is the direct result of changes in diet and other features of lifestyle and increased life expectancy [7]. A similar phenomenon can also be observed in the development of diabetes in "affluent" zoo-housed monkeys [7] and of hypertension in chimpanzees fed a high-salt diet [8].

The extremely slow pace of genetic evolution is revealed by biomolecular evidence indicating that humans and chimpanzees differ genetically by only 1.6%, although the hominoid-pongoid divergence occurred 7 million years ago [9]. If we assume that present-day hominoids are still faced with the same selection pressures that applied to humans during the millennia of evolution, there are good reasons to believe that the genes relevant to the thrifty genotype are highly conserved in these species and probably represent the "original version" of these genes common to early hominids. Thus, individuals or populations in whom a large proportion of these ancestral thrifty genes remains conserved are more likely to express the disease phenotype on exposure to a rich evironment than individuals or populations in whom less thrifty variants of these genes have recently developed [7].

This idea has substantial implications on our approach towards understanding and studying the genetic basis of these complex diseases. Currently most investigators are attempting to find the "mutations" or genetic "defects" responsible for obesity, hypertension, or NIDDM. The thrifty-genotype hypothesis, however, implies that the genetic basis for these diseases is not to be found in recent mutations or genetic defects but rather lies in the conservation of the ancestral version of the relevant genes. Thus, while the original version of the thrifty genotype may confer increased susceptibility to hypertension or obesity, recent mutations resulting in a loss of "thriftiness" would protect the lucky carrier from the deleterious effects of hamburgers and salted French fries.

A fine example of this principle was recently provided by the study of the angiotensinogen gene in human hypertension. In 1992 Jeunemaitre and coworkers [10] reported a genetic variant of this gene involving the substitution of threonine (T) for methionine (M) at codon 235 to be more common in hypertensives than in normotensive controls. Assuming that the rarer T allele associated with hypertension was the novel form, they termed this variant M235T, suggesting that M is the ancestral allele and T the mutation. However, subsequent studies in Japanese [11] and African-Americans [12] have revealed that this mutation is much more common in these populations than in whites (Fig. 1), and other investigators have found this variant to be even more common in Nigerians, in whom it approaches a frequency above 90% [13]. Since the ancestors of present-day whites are believed to have migrated from Africa, it soon became apparent that the T at codon 235, associated with hypertension is the wild type whereas the M allele, associated with normotension, is the recent mutant. This idea was further supported by the demonstration that the T at codon 235 is present in a variety of primates, including man's closest relative, the chimpanzee [14]. This would indeed be in line with the concept that the original phylogenetically ancestral version of the angiotensinogen gene is associated with hypertension, whereas the recent mutation somehow decreases the risk for developing high blood pressure. As complex genetic diseases such as hypertension are likely to involve many genes and a host of environmental factors, it is not unlikely that similar observations will be made for other genes.

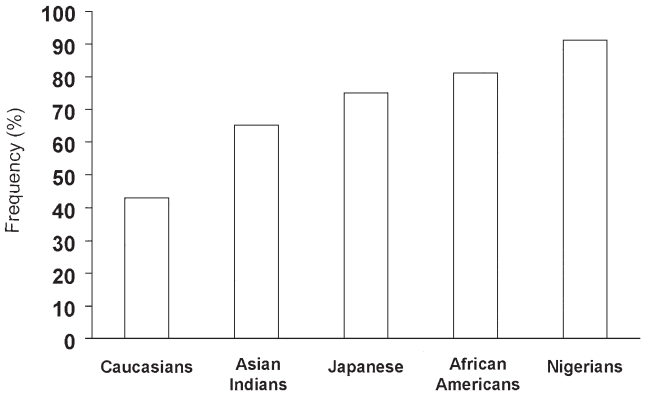

Fig. 1 Frequency of the *AGT* 235T variant in various ethnic groups

There may be a message to be learned in this. Rather than continuing to look for putative disease-causing "mutations" common to the majority of individuals with *essential* hypertension, it might be more rewarding to look for mutations that cause "resistance" to this disease despite exposure to the same detrimental environment. Thus, for example, salt-sensitive individuals who experience a rise in blood pressure under a high-salt diet may represent the normal phenotype, whereas salt resistance is due to mutations of salt-conserving genes. These protective variants will likely prove to be of recent origin and thus explain the low prevalence of hypertension in certain populations. In contrast, it is likely that the high prevalence of hypertension in certain populations will prove to be due to a conservation of the original "thrifty" version of the relevant genes. Identification of these protective variants of certain genes will ultimately help delineate the importance of these genes for blood pressure control and the development of hypertension. A similar

approach may also prove rewarding with regard to understanding the genetic basis of obesity, NIDDM, and other diseases of civilization.

One obvious drawback to this approach is that a large number of variants leading to a less than optimal "thriftiness" of a variety of candidate genes are likely to be encountered among resistant individuals. This is simply because random mutations to a gene are generally more likely to have detrimental than beneficial effects on the biological function of the gene. A further complexity is clearly added by the fact that epistatic interaction between genes makes it likely that genetic variation in one gene affects the adaptive qualities of mutations in another gene. If the protective influence attributable to these variants is relatively low, searching for the responsible genes through conventional linkage studies may prove hopeless [15]. As recently pointed out by Risch and Merikangas [15], association studies examining the relative frequencies of polymorphisms within candidate genes will prove to be a more rationale and powerful approach. It must, however, be expected that within any given candidate gene a relatively large number of polymorphisms can be identified, of which only a minority are likely to have important biological effects, especially with regard to promoting or retarding the development of the relevant disease phenotype.

At this point comparative studies of hominoid genes aimed at describing the original thrifty genotype may prove convenient. If we assume that those domains of a gene that are essential for its optimal (thrifty) function are conserved in both present-day humanoids and affected humans, the thrifty or original version of the gene represents those gene sequences that are common to humanoids and affected individuals (Fig. 2). On the other hand, variants which are present only in either humanoids or affected humans presumably represent random deviations from the original version and are thus unlikely to be of relevance for the expression of the thrifty genotype. These variants can hence be ignored as regards susceptibility to the disease in question. Once the most parsimonious consensus sequence corresponding to the ancestral (thrifty) version of the gene has been defined, this information can be used to identify variations from this sequence present only in unaffected individuals. Obviously such variants could well be of functional significance for the disease resistance found in these individuals. Conversely, areas of the "thrifty" sequence that appear highly conserved among affected individuals, and by definition are also conserved in humanoids, are likely to represent domains of the gene that are of fundamental importance for its "thriftiness", and thus for its disease-promoting function.

As presented in the above example with regard to hypertension and the angiotensinogen gene, the hypothesis that disease-susceptibility variants for common diseases of civilization represent the ancestral version of the thrifty genotype is directly amenable to testing. This can easily be accomplished by searching for the human poly-

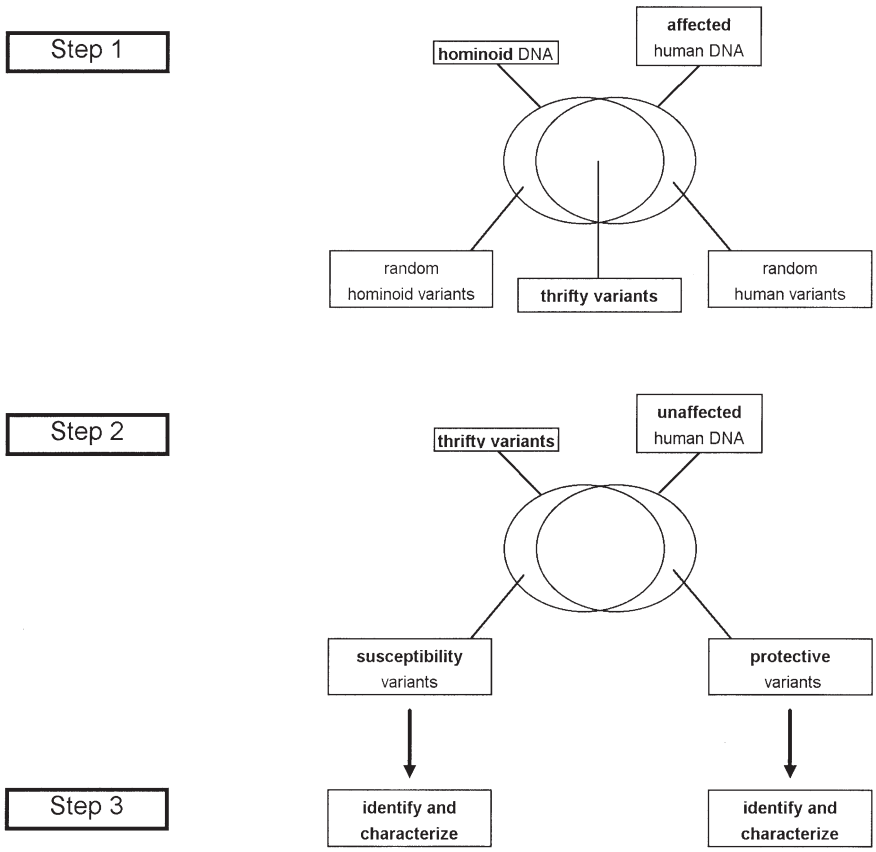

Fig. 2 Gene-identification strategy. *Step 1:* Identify allelic variants common to both affected individuals and present-day hominoids. *Step 2:* Compare allelic variants of unaffected individuals with those common to affected individuals and hominoids. *Step 3a:* Identify and characterize *susceptibility* variants common to affected individuals and hominoids but absent in unaffected individuals. *Step 3b:* Identify and characterize *protective* variants present in unaffected individuals but absent in affected individuals and hominoids

morphisms that have so far been associated with these diseases in the genetic code of primates. As in the case of the 235T variant of the angiotensinogen gene, variants that are also present in primates are more likely to be truly related to a risk for the disease phenotype than variants of recent origin. Furthermore, the study of slender, normotensive, and nondiabetic individuals in populations in which obesity, hypertension, and NIDDM are rampant may provide important insights into the pathogenesis of these entities. Thus acceptance of the thrifty-genotype hypothesis should prompt a reversal of the definition of cases and controls, thereby resulting in a paradigm shift in our approach towards studying the genetic basis of these diseases.

This approach to the study of complex diseases of civilization does of course not rule out that in rare instances recent mutations result in the development of monogenetic forms of obesity, hypertension, or diabetes in some individuals [16]. These can still be addressed by conventional linkage approaches in families and will certainly help identify candidate genes with important functions in metabolism or blood pressure homeostasis.

References

1. Neel JV (1962) Diabetes mellitus: a thrifty genotype rendered detrimental by progress? Am J Hum Genet 14:353–362
2. Murray CJ, Lopez AD (1996) Evidence-based health policy – lessons from the Global Burden of Disease Study. Science 274:740–743
3. Lappé M (1994) Evolutionary medicine. Sierra club books, San Francisco, p 55
4. Eaton SB, Konner M, Shostak M (1988) Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. Am J Med 84:739–749
5. Milton K (1993) Diet and primate evolution. Sci Am August: 70–79
6. Eaton SB, Konner M (1985) Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 312: 283–289
7. Diamond JM (1992) Human evolution. Diabetes running wild. Nature 357:362–363
8. Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, Moisson P, Pingard AM, Shade R, Carey D, Ardaillou R, Paillard F, Chapman J, Thillet J, Michel JB (1995) The effect of increased salt intake on blood pressure of chimpanzees. Nature Med 1:1009–1016
9. Sibley CG, Ahlquist JE (1984) The phylogeny of the hominoid primates, as indicated by DNA-DNA hybridisation. J Mol Evol 20:2–15
10. Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel JM, Corvol P (1992) Molecular basis of human hypertension: role of angiotensinogen. Cell 71:169–180
11. Hata A, Namikawa C, Sasaki M, Sato K, Nakamura T, Tamura K, Lalouel J-M (1994) Angiotensinogen as a risk factor for essential hypertension in Japan. J Clin Invest 93:1285–1287
12. Rotimi C, Morrison L, Cooper R, Oyejide C, Effiong E, Ladipo M, Osotemihen B, Ward R (1994) Angiotensinogen gene in human hypertension: lack of an association of the 235T allele among African Americans. Hypertension 24:591–594
13. Rotimi C, Puras A, Cooper R, McFarlane-Anderson N, Forrester T, Ogunbiyi O, Morrison L, Ward R (1996) Polymorphisms of renin-angiotensin genes among Nigerians, Jamaicans, and African Americans. Hypertension 27:558–563
14. Inoue I, Nakajima T, Williams CS, Quackenbush J, Puryear R, Powers M, Cheng T, Ludwig EH, Sharma AM, Hata A, Jeunemaitre X, Lalouel JM (1997) A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription. J Clin Invest 99: 1786–1797
15. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273:1516–1517
16. Lander ES, Schork NJ (1994) Genetic dissection of complex traits. Science 265:2037–2048