The Thrifty Gene Hypothesis: Considering the Significance of a 47-year old Theory

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"If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic selection against the condition? If, on the other hand, this frequency is a relatively recent phenomenon, what changes in the environment are responsible for the increase?"

James V. Neel, 1962

In a 1962 article first published in The American Journal of Human Genetics, James Neel put forward a novel hypothesis to explain the growing incidence of diabetes mellitus in the mid-20th century human population. At the time, the epidemiology of the budding diabetes epidemic was ill defined, and the confounding variables to explain its growing prevalence were actively sought after. The huge proportion of patients afflicted with diabetes and related metabolic disorders was counterintuitive to researchers, for it seemed that these diseases would have hindered reproductive vitality and acted as a negative selection factor over the course of human evolution. To explain their persistence, Neel suggested that a "thrifty genotype," which modified the regulation of insulin release and glucose storage may have provided a survival advantage for some of our hunter-gatherer predecessors. This metabolic profile would have permitted these individuals to match cycles of feast and famine with proportionately large fluctuations in blood insulin levels, allowing them to efficiently store excess energy and better survive through periods of famine and food scarcity. However, now given modern Western society's plentiful food supply, this genetic disposition has come to be detrimental to the descendents of these individuals. The hypothesis proposes that this thrifty genotype in the modern abundant food environment may be responsible for the elevated insulin levels and excessive energy stores in some type-II diabetic individuals, and has contributed to the insulin resistance and obesity that has come to characterize many of these patients.

Several areas of research have laid support for the thrifty gene hypothesis. Archaeological evidence has shown that it was common for Late-Paleolithic human ancestors to experience alternating periods of food abundance and scarcity. Research on the dietary habits of modern Native Americans has also shown that the descendents of tribes that experienced extended periods of food deprivation are at an increased risk for developing diabetes compared to descendents from tribes that had a more steady food supply. Despite these anthropologic and archeological discoveries, Neel’s theory is far from being universally accepted and is still a contested topic in many areas of study. Skeptics argue that while the theory provides a satisfactory explanation for the genesis of diabetes and metabolic disorders presently facing the developed world, not a single convincing thrifty gene has yet to be discovered. Other authors present a more philosophical contention with the theory, and have put forward their own criteria and definitions of the hypothesis. The following is an update on recent thrifty gene discoveries and a review of one of the main arguments that has been made against the thrifty gene hypothesis, with hopes to clarify the purpose of the debate surrounding this 47-year-old theory.
Two recent Thrifty Gene Discoveries and the Arguments against Them

Genomic regions related to insulin signaling pathways, sensitivity, production, response, and regulation are obvious candidates for thrifty gene research due to their central involvement in regulating circulating glucose levels and the great variance they show between different races and ancestral lineages. One sequence that has been of particular interest recently is the insulin variable number of tandem repeats (INS-VNTR). This microsatellite is found in the insulin gene promoter region and has shown great variance between African and non-African populations. Individuals of non-African heritage display three variations of this sequence, whereas African populations display over twenty-one classes of INS-VNTR. Such genomic variation between populations has been a purported characteristic of thrifty genes, as it may explain the higher incidence of diabetes in particular population groups. Further research on INS-VNTR has supported this suggestion by demonstrating correlations between INS-VNTR, diabetes, and higher birth weight, which is a known risk factor for the onset of diabetes later in life.

A second genomic region that has recently been claimed to possess ‘thrifty’ qualities is the gene encoding for ApoE, the main lipoprotein incorporated into the chylomicron surface. Great variation is seen in the geographical distribution of ApoE forms. ApoE2 is seen predominantly in Mediterranean populations, whereas ApoE4, the variant correlated with an increased risk of cardiovascular disease, is commonly seen in Aboriginals and Native Americans. It has been argued that the ApoE gene is a thrifty gene because particular variants improve fertility by promoting steroid production, and population studies have shown that women who possess ApoE4 have more children than women with ApoE2.

Despite these recent studies in support of the thrifty gene hypothesis, the theory is still met by a great deal of skepticism. One of the aforementioned reasons is that, while the theory is harmonious with the principles of natural selection, in over 40 years not a single thrifty gene has been found without some element of controversy or refutation. Even in the two examples just described, further research replicating the purported ‘thrifty’ nature of INS-VNTR and ApoE have either been unsuccessful or so limited that no conclusions can yet be made.

Other Arguments Against the Hypothesis

Others have challenged the theory on more theoretical grounds. In 1992, Nicholas Hales and David Barker proposed what was considered to be a contradictory theory to the thrifty gene hypothesis. Calling it the thrifty phenotype, they suggested that an individual’s metabolic profile is determined not by their genetic composition, but rather by the environmental cues during the early periods of life. The phenotype theory claims that the nutrition of a baby during fetal and early postpartum life will shape the efficiency of that individual’s metabolism into their adolescent and adult life. For example, if a woman experiences periods of malnutrition or famine during her pregnancy, the development of her unborn child will be modified in such a way that it will be metabolically attuned after it is born to an environment that is short on food. Given this metabolic profile, the child will have a greater chance of survival in a setting that is lacking adequate food resources or that undergoes bouts of famine. But, if at any point in their life their situation changes and they are in an environment of persistent nutritional affluence, their modified metabolism will prove detrimental in much the same way a thrifty genotype would.
One study tested the thrifty phenotype hypothesis in Gambia, a country that has experienced significant periods of food shortage in recent history.\(^9\) It was shown that malnourishment during fetal life was a positive adaptation and improved subsequent child survival upon birth, insofar as the “circumstances in later life continued to match those that have induced the initial adaptation.”\(^9\) This was an important point, because it was found that many individuals who experienced nutritional deficiencies during their early youth would often relocate to urban environments in search of jobs later in life. An unfortunate consequence of this understandable goal was that they were inserting themselves into an environment that had a more steady food supply. These individuals were shown to develop metabolic disorders at a higher rate than their counterparts who did not experience nutritional deficiencies during their fetal life.\(^10\) Furthermore, individuals within the rural Gambian population who were born into nutritional hardship and stayed in such an environment were shown to develop diabetes and cardiovascular disease to a much lesser extent than those who moved to urban environments.\(^11\) Additional studies have shown that nutritional hardship experienced by a fetus is the most important variable in determining metabolism and fetal growth,\(^12\) and famines that stunt the growth of the mother during her own infancy and childhood can influence the development of her child years later.\(^13\)

**Thoughts on Genotype vs. Phenotype and the Debate Itself**

There are several issues that hinder the debate surrounding the thrifty gene hypothesis. First, when contrasting the genotype and phenotype theories, it must be appreciated that the phenotype theory is at an inherent advantage given the complexity of fetal development. While there are numerous genomic techniques to study the function and regulation of a purported ‘thrifty’ gene, there are equally as many variables of pregnancy and development that can ultimately influence the metabolism of a newborn. The thrifty phenotype claims that an individual’s metabolism can be shaped based on the availability of food going back to when the individual’s mother was an infant, and what her nutritional status was like during her formative years. This provides the phenotype hypothesis with more theoretical flexibility than could ever be permitted for the thrifty gene hypothesis, as it covers such a broad span of time during which so many other factors may be at work. A second point is that while the phenotype theory has been presented as being contradictory to Neel’s genotype hypothesis, it has not been completely shown why these two theories are necessarily mutually exclusive. Both are reasonable explanations for the epidemic of metabolic disorders in modern society, and it would be unreasonable to assume that there is only a genetic or environmental root to complex disorders of insulin regulation and glucose storage.

Another difficulty that hinders the debate is the lack of consistency in what can or cannot be considered a thrifty gene. Skeptics seem to have a very narrow definition of a thrifty gene: that it must show positive selection dating back to our early ancestors, or that it must be directly related to insulin sensitivity and energy storage.\(^5,6\) On the other hand, proponents of the genotype hypothesis have a more liberal definition of what could be a thrifty gene, and have even broadened the theory to apply to cardiovascular conditioning and exercise.\(^14\) It is clear that before there is any resolution to the debate, certain characteristics must first be agreed upon that can be used as criteria to deem a particular gene thrifty.

There is much work to be done in clarifying the ongoing thrifty gene debate. A defined set of criteria for purported thrifty genes must be made, and both sides must come to appreciate that
there is very likely both a genotypic and phenotypic component to diabetes, obesity and the metabolic syndrome. But in a broader sense, the central goal of the debate should not be lost; for the purpose of the research is not just to determine if one hypothesis is valid or if a particular gene is 'thrifty.' Rather, the goal should be to better appreciate what implications a ‘thrifty’ designation has on our understanding of the function and regulation of a gene, so that we may better understand the complex nature of diabetes and metabolic disorders as a whole.

REFERENCES