THRIFTY GENE: AN EVLUTIONARY TWIST IN OUR GENOME

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Abstract:

Over 47 years ago, Neel had hypothesized about thrifty gene as those genes which enabled individuals to process food efficiently and store as fat during periods of food abundance and use it during famine. He hypothesized that these essential protective alleles of ancient times have become detrimental in the present times due to natural selection. In this article we have discussed about various thrifty genes and also analyzed its effects in causing complex diseases such as obesity and Type 2 Diabetes Mellitus. We have also analyzed genes like CRP and PPARγ in how they contribute to the Thrifty Gene Hypothesis. We have tried to present a detailed insight of arguments for and against the theory of thrifty genes in this article. Eventually, we have observed that this thrifty gene hypothesis is not in alignment with medical reasoning.

Introduction

Thrifty genes are those genes which enable individuals to efficiently store and process food so as to deposit fat (beneficial in ancient times but detrimental in modern times) during periods of food abundance. Alleles which were essential in ancient times now have become detrimental with evolution due to present day lifestyle and environmental changes leading to diseases like obesity and Type 2 diabetes mellitus (T2DM). Those genes containing these alleles are known as thrifty genes. James Neel in 1966 proposed thrifty gene hypothesis which states that populations whose ancestral environments were characterized by periods of feast and feminine experienced positive selection for thrifty genes. Under present day conditions, populations with such thrifty metabolisms are expected to have high rates of diabetes and obesity (e.g. Pima Indians). For a gene to be characterized as a thrifty gene, it must be able to exhibit two important features. Firstly, it must show flexibility or plasticity in accordance with environmental circumstances. Secondly, it must conform to both positive and negative selection cycles across geographical distributions over large evolutionary time period. Examples are sickle cell anemia, cystic fibrosis, T2DM and obesity. A gene which is thrifty, it should always remain in operative mode and thus lead to obesity. In this scenario, even though extra fat stores would cause survival during times of famine which can be viewed as a positive cycle but on the other hand these extra fat reserves would lead to obesity and hinder reproductive functions in both males and females alike. (Prentice et al 2005)

Examples of Common Diseases which support Thrifty Gene Hypothesis (TGH):

(i) Sickle Cell Anaemia

Sickle cell anemia occurs due to a point mutation which occurs due to amino acid mutation at sixth position on β-hemoglobin chain by replacing *glutamic acid* with *valine* and thus producing abnormal hemoglobin type Hb^S (Hb^A is normal). This causes the red blood cells to be sickle shaped by giving up oxygen to tissues. As a consequence, those homozygous individuals having Hb^S(Hb^S/Hb^S) develop sickle cell disease. Just like T2DM and obesity, sickle cell disease has evolved evolutionary. The gene for sickle cell disease survived through positive selection as a beneficial gene. This is due to its effect in counteracting malaria. It is known fact that heterozygous (Hb^S/Hb^A) having both types of hemoglobin can resist malarial infection by targeting infected cells for destruction. On the other hand, individuals homozygous for normal Hb(Hb^A/Hb^A) are targeted by malaria. Hence, this allele survived in heterozygous who are more protected than either of two homozygous forms (i.e. Hb^A/Hb^A and Hb^S/Hb^S). Evolutionary this allele confers a balancing selection which is a special type of natural selection that operates on keeping two or more beneficial alleles at relatively high frequency (Harris and Malyango 2004; Prentice et al 2005).

(ii) Cystic Fibrosis

Cystic fibrosis (CFTR) is caused by a genetic defect encoding a gene which codes for chloride ion protein channels on epithelial cell membrane but protected against bacteria causing Typhoid fever. Just like sickle cell anemia, Typhoid infection is markedly reduced in heterozygous forms (who have reduced expression of CFTR on cell surface). So, homozygous for one type (i.e normal CFTR) allele are targeted by Typhoid infection but on the other hand , those who are homozygous for mutant CFTR allele/gene (delta F508 CRTR) suffer from cystic fibrosis. Thus, mutant allele has survived through evolution (Harris and Malyango 2004; Prentice et al 2005). Hence, this allele acts as a protective allele in heterozygous form and as a result survived in nature as a rare allele. Natural selection might have adapted our genes (diseased) in such a way that it is advantageous in a particular environment.

Examples of Thrifty Genes:

(i) CRP

Considering the thrifty genotype hypothesis, the ancestral version of the alleles proves to be deleterious in the present day environment while the rarer alleles which may have protective effects against the disease have evolved lately (Sharma AM, 1998). Fernandez-Real and Ricart have implicated the role of genes encoding for cytokine synthesis as thrifty genes (Fernandez-Real J.M and Ricart, 1999). They hypothesized that higher secretion of cytokines and increased acute phase response were an evolutionary adaptation to phases of acute infections and trauma. In the ancestral period, outbreaks due to infections were higher. Simultaneously due to exposure to

famines, metabolic pathways favored insulin resistance to survive in low food situations. It has been proposed that insulin resistance and cytokine responder genotypes were favorable adaptations to low fat, high fiber and high physical activity environment. The genomes of the present day human are still genetically adapted to ancestral conditions which are designed to fight against infection with minimal food intakes and high physical activity. However, environmental transition is more rapid, and evolution being a slow process, our genotypes have not modified according to the present day environments of lower infections, availability of surplus food and low physical activity. In the absence of the favorable conditions and with advancement of age, insulin resistance ensues which further activates inflammatory cascade that eventually results in atherosclerosis. Thus, in the presence of insulin resistance genotypes and western lifestyle, a high cytokine responder genotype would be more prone to develop T2D and atherosclerosis. (Fernandez-Real and Pickup 2007, Fernandez-Real and Ricart 1999, Sharma 1998).

(ii) PPARγ

Normal PPARγ acts as a thrifty gene causing obesity, adipocyte hypertrophy and hence induces factors such as TNFα and fatty acids leading to IR. It has been hypothesized that a protective polymorphism, particularly Pro12Ala by substitution of *Proline* to *Alanine*, caused protection from development of T2DM. The Ala allele is found to help only those who are at risk of T2DM but not in those who already have T2DM. Pro12Ala is the result of missense mutation of CCA to GCA at codon 12 of exon B. The *Ala* variant of PPARγ causes enhanced suppression of lipolysis, resulting in decrease release of fatty acids. This in turn causes uptake of glucose from blood into muscle and liver tissues and thereby decreasing risk of T2DM in these people. *Ala* causes reduced transcription of certain genes like oxidase and lipase when compared to wild type protein. Also, it is important to note that activity of PPARγ promotes breakdown of large adipocytes into small adipocytes by differentiation which are more insulin sensitive. In presence of Ala, there is alteration of white adipose tissue, triglycerides (TG), hepatic TG and energy consumption thereby enhancing insulin effect. The net result of amino acid exchange, particularly *Ala*, leads to enhanced anti-diabetic effect of PPARγ (Kadowaki et al 2003, Stumvoll and Haring 2002).

PPARγ is an important component of thrifty gene as it plays a pivotal role in mediating high fat induced obesity and also causes insulin resistance under same conditions. It is now known that two alleles of PPARγ might interact with environment in a negative way to cause T2DM. Here, the occurrence of Ala (C) allele undergoes a conformational change in the protein which positively affects its activity. Ala12 has reduced transactivation and this allele is highly conserved and acts as a protective allele for T2DM. This allele exists in codon 12 and also enhances insulin sensitivity as compared to those obese people who lacks Ala12. This alanine allele (C allele) protects against insulin resistance in otherwise obese subjects. This positive mutational change may be due to interaction of PPARγ gene with both genetic and environmental factors leading to insulin sensitivity in obese people having it versus those obese people lacking it (Kadowaki et al, 2003).

Neel (1962) proposed that certain genes (such as PPARγ and CRP) have survived through natural selection which favoured in ancestral conditions. Thus, this hypothesis justifies how humans were able to adapt and colonize different diverse environments. This acknowledges that there are several genetic factors to explain thrift in humans, such as (i) a genetic pattern common to all humans (such as vis Pro12Ala and CRP mutation) and (ii) contemporary difference among general population.

Obesity and T2DM as outcomes of thrifty genotypes

Diabetes and obesity also follow Thrifty gene characteristics similar to sickle cell anemia and cystic fibrosis (that is, shift from positive cycle to negative cycle). The Thrifty Genotype Hypothesis (TGH) states that diabetes just like sickle cell anemia and cystic fibrosis might have evolved as a positive adaptive trait in certain environmental conditions but which later turned detrimental due to changes in life-style. Thus, according to Neel, the thrifty genotype had helped during feast and feminine days of early evolutionary period but presently turned detrimental in modern period of continuous feasting.

Insulin resistance which leads to T2DM have evolved not only genetically but also evolutionary which evolved as an adaptive trait but now turned pathological due to lifestyle changes. Thus, it has been suggested that such modification in modern man in terms of lifestyle and diet have given rise to epidemic diseases such as T2DM (Neel 1962, Neel 1998). One of the major risk factors for CVD and T2DM is the association between obesity and inflammatory markers, such as CRP. It is known that pro-inflammatory state which is associated with obesity provides an impetus for development of T2DM and CVD alike. According to thrifty gene hypothesis, genetic selection favours those people who have a greater capacity to store energy (food) conserving genotypes in such harsh environments. Thus due to evolution, selective genetic variations which favoured malnourished people in the past now is detrimental particularly when nutrition improved in modern era. Eventually under modern era, these genes caused MetS under various ethnic groups.

South Asians are more prone to insulin resistance as well as T2DM than other counterparts. According to Neel's postulate (Neel, 1962), it might be possible that South Asians stored visceral fat which can be more easily utilized, thus providing a selective advantage when food sources were scarce. In addition to this, the pro-inflammatory cytokines increased the livelihood of children particularly those suffering from infections due to either pathogens or parasites. Hence, these thrifty genes and storage of fat as visceral adipose tissues (VATs) has become a liability in due course to the population who are living a sedentary lifestyle with abundant food supplies. However, this explanation based on TGH cannot explain about other ethnic populations facing the same risk of T2DM even though these ethnic groups were subject to similar environmental changes over the past few centuries. One possible explanation could be that European population shifted from a primitive agricultural lifestyle and became modernized much earlier such that their genes could adapt to these changes more readily when compared to their South Asian and other ethnic counterparts, which took relatively longer time to adapt to urbanization from a primitive

agricultural lifestyle. Thus thrifty genes proved to be a selective advantage in South Asians when compared to their European counterparts (Bakker 2013; Hall et al, 2008; Prentice et al, 2005).

As a consequence of this drastic change those advantaged early alleles in ancient times are now being placed in an environment of sedentary lifestyles, high fat and poor fibre diet resulting in positive caloric imbalance along with extended life-span, all of which caused protective alleles to be delirious now and its mutant alleles now became protective alleles (Chakraborty and Booth 2004, Watve and Yajnik 2007, Joffe and Zimmat 1998). This can also be the result of characteristic difference between ancestral and modern man in that muscles of modern man are now fattier than ancestral man and thus has resulted in different attributes of skeleton muscle cells/tissues to utilise insulin well in ancestral man compared to modern man. This along with high carbohydrate diet leading to increased sugar and hence, enhanced T2DM risk [Neel, 1998; Lesley et al, 2008]. Again, total energy expenditure of modern man was no match when compared to ancestors (that is 3000 Kcal/day by ancestors to 2000 Kcal/day by modern humans). Again, another point to take into account is our diet which involves high carbohydrate leading to increased sugar and hence, enhanced T2DM risk (Neel JV, 1998).

It is well-known that T2DM is disadvantageous; however its alleles have existed throughout evolution. Since TGH is very much associated with natural selection, then natural selection has given rise to two vital concepts for their diseased alleles to survive throughout evolution. These are as follows:

(i) The risk variant/alleles might be derived from evolutionary perspective which is effectively neutral based on most of the occurrences are generally small and only manifest in old-age. This might be due to genetic drift. These diseased alleles might have some advantage, either now or past such that due to positive selection these alleles are still high in frequency.
(ii) The second one is due to Neel's thrifty gene hypothesis which resulted in T2DM alleles survive from evolutionary origin. (Ayub and Chen et al. 2014).

Frequency of T2DM alleles:

(i) Obesity was rare in ancient environment than present environment.
(ii) Action of adrenal steroids causes subclinical T2DM apart from its effect on gluconeogenesis.
(iii) Decrease in physical activity to counteract enhanced insulin secretion. These last two reasons are important for T2DM development (Neel, 1999).

Based on two main assumptions, (i) reducing energy needs through both physical/behavioral alternation or (ii) storing energy effectively rather than use it; then this is known as thrifty trait acquired by these animals. Later on this became known as metabolic thrift which may either manifest itself through natural selection of genetic factors or through evolutionary and constant movement through life-course experience. It should also be taken into account that unlike other

species, mammals can utilize energy stores effectively so as to avoid fluctuations of energy needed in moving from one place to another place (migration).

The emergence / evolution of human race were due to unequal distribution of thrifty genes within humans. Even though Neel claimed that such thrifty genes were proven advantageous during famine in distant past times but this phenomenon is now doubted. Recent evidence of human genome suggests that genetic variability occurred due to adverse climate change/factors which resulted in humans leaving out of Africa. Changes in dietary exposures have resulted in SNP's relevant to energy have emerged and there seems to link this to adiposity (via Pro12Ala polymorphism) in contemporary populations. It has now been postulated that human adiposity (through PPARγ) is the main root cause of global obesity epidemic and its variable manifestation across different ecological environments. It should be noted that it is of prime importance to determine thrifty genotype between its generation and transfer between and within generations (passing on) to determine how human evolution progressed.

Due to existence of genetic variability, human classification as per energy utility like other mammals are very complex. Neel defined thrifty genes for those ancestral people who could utilise energy and consume food effectively in diverse environments and also suggested that these genes helped only a minority of human population, particularly those that were readily exposed to regular 'feast and famine' cycles.

Arguments in favour of Thrifty Gene Hypothesis

Civilization also along with environmental stress factors has always favored the thrifty genotype.

(1) Agricultural population are less susceptible to food stress and feminine than ancestral population, which is contrary to the belief that agricultural population are more prone to food shortage and feminine.
(2) The dietary history of Europe where thrifty genotype is least common indicating an interesting and novel phenomenon that this occurs under food stress much like during the times of Romans, Anglo-Saxon and other medieval periods.

Famine has been a common feature/trait for a long time and as a consequence of famine, people faced numerous deprivations with enhanced mortality rate. This has been evidenced by many records of famine which occurred 5000 years ago. Even now, famine continues to affect human populations. The evolution of advantageous allele is dependent on selection and also on the frequency at which such selection takes place. It should be noted that periods of starvation (due to famines and shortage of food supply) occurred frequently. This is possible because obese individuals store much greater amounts of energy and are more evolutionary adaptable than lean people and so can live longer during famine period. Thus, obese people would have a selective advantage over lean people in an evolutionary survival phase (Speakman 2006).

Another example is the need to quench oxidative stress by mitochondria due to reduced substrates. Brand and colleagues (Brand 2000) have proven that all mammalian organisms have a high rate of proton leakage across mitochondrial inner membrane. Brand (2000) argued that this inefficiency is necessary so as to counteract the enhanced reactive oxygen species which occurs during normal mitochondrial metabolism. Another reason for such occurrence of thrifty genes is that organisms might need to burn off (utilize) energy in concentrate diets in times of inadequate protein or micro-nutrients. These examples show that such traits have been selected in these organisms so as to survive and perform optimum function in times of need (Prentice et al 2005).

There are some other examples of arguments for thrifty gene since thrifty genes have evolved evolutionarily. One of them is involving birth canal. The pelvis of female is different to males in that females have a rounder pelvic to assist in birth canal opening during child birth. Evolutionarily the brain of modern man has evolved many generations ago. However, the pelvic of females did not evolve as such to assist in child birth due to bipedalism (walking on two feet). Exceptional increase in birth canal would have caused bipedalism to be mechanically and energetically unfavourable. Thus, overall size of birth canal could be viewed as an evolutionary compromise between brain size and bipedalism.

Another example is that natural selection promotes reproductive success but not necessarily health lead to explaining certain genes due to compensating advantage. For example, PKU in homozygotes develops mental retardation as they cannot metabolize phenylalanine but in heterozygotes this genes reduces probability of miscarriage. Another example is hemochromatosis which is characterized by enhanced intestinal iron absorption. It has been hypothesized that gene might be advantageous in women due to compensation of huge iron losses but in men with this gene might suffer from excessive iron stores in later life. This gene has survived as individuals having C282Y mutations show resistance to Yersinia bacterium causing plaque. In normal people, Yersinia could multiple within iron rich macrophage but it does not occur in people with C282Y as these people lack iron, a mineral essential for pathogen survival. Thus, natural selection favoured persons bearing C282Y allele during plaque (Harris and Malyango 2005).

Arguments against Thrifty Gene Hypothesis

On the other hand, there are reasons to explain the occurrence of non-thrifty genotypes as well:

(1) Traditional explanation: It is absent in Europe because they probably had westernized diet and explanation as per thrifty hypothesis.

(2) Chance: This genotype has been lost in these populations due to factors such as environmental or genetic encounter. This explanation might flop because of favoured explanation as per thrifty hypothesis.

(3) Social factors: In a complex society access to food and especially quality food may be influenced by factors difference from those seen in early evolutionary era. Now, after a period of

food shortage, which come out to be more adaptable may depend less on metabolism and more on social and economic status. This is "luck by chance" provided that elite population is generally low.

(4) Interaction with another specific nutritional factor: The dietary factor that made difference between two populations is lactose. Lactose is a disaccharide, that is glucose + galactose (galactose can be converted to glucose) gives rise to two glucose units. This in turn increases diabetes. It is absorbed in the blood and is metabolized as simple sugar. Again, insulin response to lactose and hence glucose is very high. Difference between westernized diets, leading to enhanced glucose being produced which in turn leads to T2DM. (Allen and Cheer 1995)

Firstly, the extent of mortality during famine and its frequency are insufficient. It should be taken into account that numbers that die are frequently reported, however population they stem from are not. Thus, smaller area the estimates of mortality gets larger and larger areas which are more likely closed to emigration and famines are generally limited in their geographical extent.

Secondly, the historical pattern of famine occurrence is incompatible with other aspects of hypothesis. Even though famine seems to have evolved 5,000 years ago but it is more likely to have evolved due to agricultural period. This might be because hunter gathering people might be less prone to famine as they had a varied lifestyle diet. However, once agriculture and stable communities developed large population became dependant on agricultural crops and since, crop production depend on whether then adverse weather conditions could cause severe problems.

Thirdly, relatively few people in famines die of starvation- that is reducing their body reserves to the point where they have run out of energy. In one instance 12% of people died from famine however, only 5% death was due to starvation. Thus, starvation-induced mortality accounted for only about 0.6% of total population per annum. The major causes of death during famine are due to infectious disease and diarrhoea. Again, many people died during famine of direct poisoning from eating poisonous plants or from ingesting carron or corposes leading to intestinal infectious and diarrhoea. Another event is consuming food of low nutritional quality which might lead to reduction of immunity among these people. Lean people would be more susceptible as their need to feed requirement would be greater due to lower energy reserves. Thus, they might be more susceptible to poisoning or bad food habit due to gut problems. There is no evidence that lean people feed more than obese people.

Fourthly, the burden of mortality in famines affects wrong individuals as there to be selection for energy efficiency. This can be evidenced that mortality falls disproportionately between young and old. For example, during famine in Bangladesh most of the affected people were young (<5) and old (>60) but for individuals in teens and early twenties were unaffected. Thus, most people who die of famine die not because of starvation but due to infectious diseases.

Finally, the obesity prevalence between famines is too low. Famines are insufficient selective force so as to evolve thrifty genes as most people during famines have BMI of 17.5 to 21.0 which

is albeit lean and so do not have inherited genes to be able to be able to weight gain or be obese (Speakman 2006).

Conclusion

Neel first hypothesized about thrifty genes as those genes which were beneficial during cycles of famine and feast but now over a period of long time became detrimental. Here, we discussed about examples of thrifty genes and its implication of modern era. We have now understood how diseases such as obesity and T2DM are outcomes of thrifty genes. Thrifty gene concept is challenged by other hypothesis such as thrifty phenotype hypothesis and it can be seen that there can be both arguments for and against the hypothesis. In short, thrifty gene hypothesis is now not considered a valid hypothesis as it is in accordance with natural selection and this does not correctly depict how predisposition to certain genes might have caused an adaptive trait which later evolved as disadvantage due to later in lifestyle. So, even though thrifty gene hypothesis suggests for certain alleles as evolved to remain in nature as positive outcomes of environment as rare protective alleles which are now in heterozygous and lethal in homozygous conditions, but it is not in alignment with medical observations.

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