

Why doesn't everyone develop type 2 diabetes?

Thousands of genes control our metabolism, and type 2 diabetes has therefore been called the geneticist's nightmare. Genome-wide association studies have not been able to reveal the mechanisms underlying the development of obesity and diabetes. However, genetic and epigenetic theories are still important for our understanding of the obesity and diabetes epidemics.

Trond Methi
methi.trond@gmail.com
Per Medbøe Thorsby

In 1962, the American geneticist James Neel (1915–2000) asked a fundamental question: Why are genes predisposing for obesity and type 2 diabetes so prevalent in the population? (1). These conditions increase morbidity and mortality, and reduce fecundity, and can hardly be reconciled with positive genetic selection. Neel's solution was an elegant and intuitive hypothesis: «Thrifty genes» which have been selected through repeated cycles of famine throughout human history, and predispose for increased storage of fat. Today's increased prevalence of obesity and type 2 diabetes is simply the result of a mismatch between what was once a beneficial adaptation for our ancestors, and current westernised societies where famines do not occur.

«Drifty Genotype»

According to the English biologist Thomas Huxley (1825–95), «Every beautiful hypothesis can be slain by an ugly fact» (2). If the storage of fat was so beneficial for our ancestors, why isn't everyone in the western world obese? Mathematical models have shown that there have probably been enough famines for thrifty genes to be completely fixed in the population (3). However, not everybody who lives a western lifestyle is obese, and therefore the hypothesis collapses, or at least does not tell the entire truth. Even in the USA, the cradle of the western lifestyle, one-third of the population is of normal body weight. Given the unlimited supply of high calorie food, and the possibility of minimal physical activity, this is at least as puzzling as the one-third of obese at the opposite end of the scale.

The English biologist John Speakman has proposed an alternative explanation: «The Drifty Genotype.» Speakman argues that increased storage of fat certainly increases survival during a famine, but it

also reduces mobility, and thereby the ability to escape from predators and enemies, as well as limiting movement to new hunting grounds (4). According to Speakmann, obesity results only when this negative selection ceases to exist, that is, when reduced mobility is no longer an issue. This happened when we discovered fire, learned to make weapons, and organized ourselves in agricultural societies. In modern times this has been extended and the obesity inducing effect reinforced with the introduction of supermarkets, running water, heated houses, television, cars and sedentary office work.

Obesity is virtually absent among most species living in the wild. This is due to limited food supply, and many species will become fat given the opportunity, but not all. Some prioritise storage of energy in depots outside the body, thereby maintaining mobility. Interestingly there is an inverse correlation between brain size and fat mass among many species in nature (5). A large fat mass corresponds to smaller brain size, and vice versa. It seems that the storage of energy as body fat and storage of information in the brain may represent alternative strategies for coping with the uncertainties of life. Humans, however, do not fit into this pattern as we have large brains as well as large fat depots.

Genes, beta cells and insulin resistance

James Neel acknowledged that the thrifty genes hypothesis was problematic. No thrifty genes fulfilling the criteria have been discovered, and in Neel's own words: «Type 2 diabetes is a geneticist's nightmare» (6). Our metabolism is not controlled by a few single genes, but by a network of many thousand where small differences in effect add up to the total biochemical phenotype of the body. It is not without reason that genome-wide association studies have not yielded the anticipated results in obesity and diabetes research. In fact, the quest for genes that predispose for obesity has largely been overwhelmed by the western world's obesity epidemic, and it is now

more productive to search for the opposite: genes which promote leanness.

About 60 genes that predispose for type 2 diabetes have been identified, but they are only able explain a small percentage of the inheritable risk we know to be associated with the disease. Interestingly, the beta cell appears to be the focal point for genetic predisposition to type 2 diabetes, while insulin resistance has returned fewer hits. Autopsy studies have shown that people with type 2 diabetes have reduced beta cell volumes compared to healthy controls, while normoglycaemic obese individuals have increased beta cell volumes compared to slim individuals (7). Some people are thus able to compensate on the level of beta cells to withstand an increased caloric load, while others fail, and it is probably beta cell failure that paves the way for the metabolic collapse that characterises type 2 diabetes. In fact, insulin resistance may quite well be the natural consequence of any chronic nutrient surplus, where the cell tries to protect itself from oxidative stress and caloric intoxication (8). It is unknown why some people have beta cells which can compensate for the western lifestyle, whereas others fail, but maybe some clues can be found in Finnmark county in northern Norway in the 1960s and 1970s.

«Thrifty phenotype»

In 1986, the British doctor and epidemiologist David Barker (1938–2013) and colleagues published data from England and Wales showing an association between infant mortality and ischaemic heart disease in adulthood (9). According to Barker's hypothesis, organ development is impaired by a low caloric foetal stage, which may lead to higher risk of chronic diseases later in life. Interestingly, the Norwegian doctor Anders Forsdahl (1930–2006) observed the same phenomenon in Finnmark county in northern Norway ten years earlier (10), a story which has been excellently reviewed in the *Journal of the Norwegian Medical Association* previously (11). Barker's «Developmental origins of chronic diseases», or the «Thrifty phenotype» hypothesis, has been supported



Illustration © Superpop

by studies showing a relationship between the risk of metabolic syndrome/type 2 diabetes, and low birth weight (12, 13). Similar data have been reproduced in many places around the world, for example in Denmark, where monozygotic twins discordant for obesity and type 2 diabetes have also been shown to be discordant in birth weight (14). This is interesting since they have identical genes and have been raised in similar environments. Reduced blood supply through the placenta may explain the discrepancy in birth weight between the twins, leading to impaired organ development in one of them, and in turn a higher predisposition to disease later in life.

«Thrifty epigenotype»

Theories on epigenetic reprogramming of the foetus have been proposed in recent years. This means that you can have identical genes and no need for slow genetic evolution à la Neel, but an epigenetically regulated difference in gene transcription affected by the environment, which in turn gives rise to different phenotypes. Epigeneticist Reinhard Stöger calls it «The Thrifty Epigenotype» (15). According to this concept the child's metabolism is programmed by caloric availability in the intrauterine

environment, and it is possible, for example, to be programmed to live in a low calorie world. In this sense, the predisposition for metabolic disease may be a useful adaptation, not a pathological condition, and obesity/type 2 diabetes is the consequence if there is a mismatch between the intrauterine and the real environment into which a person is born.

Data from the Dutch hunger winter, which occurred towards the end of the Second World War, support this theory. Children who experienced caloric restriction in their mothers' wombs, with a subsequent ad libitum access to calories after the liberation, developed significantly higher body weight and more metabolic disease in adulthood compared to controls (16). Furthermore, 60 years later, epigenetic differences have been documented between the hunger cohort and controls born at the same time during the famine (17). This metabolic fingerprint seems even to be transferred epigenetically to the next generation (18).

«Maladaptive hypothesis»

Another possibility is that predisposition to obesity has never been an evolutionary advantage, but is rather the unintended

by-product of another genetic selection, in other words a maladaptation (19). Heat-generating brown adipose tissue (BAT) is an interesting candidate in this respect. It has long been known that not only newborns, but also adults have active BAT, a point which was «rediscovered» in 2009 by two papers investigating the prevalence and cold-induced activity of BAT in adults (20, 21). BAT plays a role in the energy homeostasis of the human body, and varies greatly from one person to another. There is furthermore an association between low levels of BAT activity, high BMI and poor glycaemic control (20, 21). In such a perspective it can be envisioned that those with less need for heat production throughout evolution have less brown adipose tissue, and now have higher risk of obesity and metabolic disease since they are less able to burn excess calories in the form of heat. This may explain the lower prevalence of type 2 diabetes among people with genetic origin from cold Nordic countries (22).

See Fact Box 1 for an overview of different theories.

Both farmers and hunters

A thrifty calorie-saving reprogramming of the organism may consist of many ele-

FACT BOX 1

Theories considering the genetic basis for obesity and type 2 diabetes

- *Thrifty genotype (James Neel)*: Famines throughout human history have selected for genes promoting the storage of fat to prolong survival. Obesity and type 2 diabetes are the consequences in a Western world where famines do not occur (1)
- *Drifty genotype (John Speakman)*: Obesity and type 2 diabetes are the consequences of the release from negative selection, i.e. less need for mobility to escape predators and thereby freedom for body weight to increase (4)
- *Thrifty phenotype (David Barker)*: Obesity and type 2 diabetes are the consequences of a mismatch between caloric restriction during the foetal stage, with impaired organ development, and subsequent caloric abundance (12)
- *Thrifty epigenotype (Reinhard Stöger)*: The thrifty phenotype is the result of an adaptive epigenetic reprogramming during the foetal stage; a preparation to live in a low calorie world (15)
- *Genetic maladaptation (John Speakman)*: Obesity is not an evolutionary advantage, but is the unintended by-product of another genetic selection, for example different needs for heat production, and consequently different levels of brown adipose tissue activity (19)

ments: Reduced metabolic rate, increased aptitude for inactivity, increased appetite when food is available, more sensitive beta cells and increased ability to store energy as fat. Whether these mechanisms are adaptive, epigenetically regulated adjustments to a low calorie world, and how this manifests itself in human physiology and pathophysiology is still unknown. Likewise it is unknown to what degree these causes may explain the diabetes epidemic evident in today's world. The evolutionary biologist Jared Diamond has pointed out that the prevalence of diabetes has exploded in many parts of the world, especially in populations who have abruptly transitioned from a traditional low calorie rural lifestyle, to a high calorie, urban, westernized existence (23). This is true for the Pima Indians in Arizona, the Aborigines in Australia, and Pacific islanders (for example Nauru), as well as many populations in Africa, the Middle

East and Asia, while the prevalence is relatively stable (albeit higher than 30 years ago) in the Western world. This may be because people in «the Western world» have had longer to adapt to the «Western lifestyle», for better or worse.

There are reasons to believe, paradoxically, that famines first became significant selection factors after the advent of agricultural societies (24). These societies do produce more food than the hunter-gatherers, but this leads to population growth as well as urbanisation, i.e. a population with a diminished ability to survive. Failed harvests increase the risk of famine for such societies, and this promotes the selection for obesity which fits well into an urban lifestyle where the need for physical activity and mobility is lower. The hunter-gatherers, on the other hand, avoid famine by living on a more varied diet, and being in small mobile groups which can move to new hunting grounds as needed. They cannot, however, allow themselves the luxury of a large fat mass to carry around with them. This may explain why some population groups seem to have more thrifty genes than others. Perhaps both the adaptations to agricultural and hunter-gatherer societies are represented in today's population? This may explain the large diversity in body weight we see in the western world, which ranges all the way from normal weight, to overweight, obesity and morbid obesity (25).

If we allow ourselves to view genetic survival not only as an individual project, but also in a group perspective, a large array of different adaptations which are beneficial for different sorts of risks, will increase the group's total chance of survival in a world full of unforeseen dangers, amongst them caloric intoxication. This may explain a related question: Why do some people get type 2 diabetes only when their BMIs reach morbid levels, and some not even then, while others suffer from the disease at normal body weight? A diminished ability to store fat increases the risk for metabolic disease if the caloric intake is excessive (26). The risk of caloric intoxication and type 2 diabetes is not primarily about body weight, but rather the health condition within the body.

Trond Methi (1977)

M.Sc.Pharm., Ph.D., works as a Medical Advisor for Lilly Diabetes.

The author has completed the ICMJE form, and declares the following conflicts of interest: Employee of Eli Lilly.

Per Medbø Thorsby (1964)

M.D., Ph.D., is Medical Head of Department at the Hormone Laboratory, Oslo University Hospital, Norway.

The author has completed the ICMJE form, and declares the following conflicts of interest: Lecture fees received from Siemens, Novo Nordisk, Bristol-Myers Squibb, Sanofi-Aventis and The Norwegian Diabetes Association.

References

1. Neel JV. Diabetes mellitus: a «thrifty» genotype rendered detrimental by «progress»? *Am J Hum Genet.* 1962 14: 353–62.
2. Huxley TH. *Collected Essays (1893–1894) VIII Discourses: Biological & Geological, Biogenesis and Abiogenesis.* New York, NY: Georg Olms Verlag Hildesheim; 1970: 244.
3. Speakman JR, Westerterp KR. A mathematical model of weight loss under total starvation: evidence against the thrifty-gene hypothesis. *Dis Model Mech.* 2013 6: 236–51.
4. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. *Int J Obes (Lond).* 2008 32: 1611–7.
5. Navarrete A, van Schaik CP, Isler K. Energetics and the evolution of human brain size. *Nature.* 2011 480: 91–3.
6. Neel JV. Diabetes Mellitus – a geneticist's nightmare. In: *The Genetics of Diabetes Mellitus.* Springer-Verlag 1976 p 1–11.
7. Butler AE, Janson J, Bonner-Weir S et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes.* 2003 52: 102–10.
8. Hoehn KL, Salmon AB, Hohnen-Behrens C et al. Insulin resistance is a cellular antioxidant defense mechanism. *Proc Natl Acad Sci U S A.* 2009 106: 17787–92.
9. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet.* 1986 1: 1077–81.
10. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Soc Med.* 1977 31: 91–5.
11. Vangen S, Nordhagen R, Lie, KK et al. Gjensyn med Forsdahl-Barker-hypotesen. *Tidsskr Nor Lægeforen.* 2005 125: 451–3.
12. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia.* 1992 35: 595–601.
13. Barker DJ, Hales CN, Fall CH et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia.* 1993 36: 62–7.
14. Poulsen P, Vaag AA, Kyvik KO et al. Low birth weight is associated with NIDDM in discordant monozygotic and dizygotic twin pairs. *Diabetologia.* 1997 40: 439–46.
15. Stöger R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? *Bioessays.* 2008 30: 156–66.
16. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med.* 1976 295: 349–53.
17. Heijmans BT, Tobi EW, Stein AD et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A.* 2008 105: 17046–9.
18. Veenendaal MV, Painter RC, de Rooij SR et al. Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine. *BJOG.* 2013 120: 548–53.

>>>

19. Speakman JR. Evolutionary perspectives on the obesity epidemic: adaptive, maladaptive, and neutral viewpoints. *Annu Rev Nutr.* 2013; 33: 289–317.
20. Cypess AM, Lehman S, Williams G et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009 360: 1509–17.
21. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med.* 2009 360: 1500–8.
22. Bakker LE, Boon MR, van der Linden RA et al. Brown adipose tissue volume in healthy lean south Asian adults compared with white Caucasians: a prospective, case-controlled observational study. *Lancet Diabetes Endocrinol.* 2014 2: 210–7.
23. Diamond J. The double puzzle of diabetes. *Nature.* 2003 423: 599–602.
24. Prentice AM, Rayco-Solon P, Moore SE. Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proc Nutr Soc.* 2005 64: 153–61.
25. Prentice AM, Hennig BJ, Fulford AJ. Evolutionary origins of the obesity epidemic: natural selection of thrifty genes or genetic drift following predation release? *Int J Obes (Lond).* 2008 32: 1607–10.
26. Wang MY, Grayburn P, Chen S et al. Adipogenic capacity and the susceptibility to type 2 diabetes and metabolic syndrome. *Proc Natl Acad Sci U S A.* 2008 105: 6139–44.

Received 30 July 2014, accepted 27 October 2014.

Editor: Erlend Hem.