Reviews in Endocrine and Metabolic Disorders (2019) 20:321–332
https://doi.org/10.1007/s11154-019-09505-z

Genetics, adaptation to environmental changes and archaic admixture in the pathogenesis of diabetes mellitus in Indigenous Australians

Malgorzata Monika Brzozowska[1,2] · Essi Havula[3] · Richard Benjamin Allen[4] · Murray P. Cox[5]

Published online: 5 July 2019

Abstract
Indigenous Australians are particularly affected by type 2 diabetes mellitus (T2D) due to both their genetic susceptibility and a range of environmental and lifestyle risk factors. Recent genetic studies link predisposition to some diseases, including T2D, to alleles acquired from archaic hominins, such as Neanderthals and Denisovans, which persist in the genomes of modern humans today. Indo-Pacific human populations, including Indigenous Australians, remain extremely underrepresented in genomic research with a paucity of data examining the impact of Denisovan or Neanderthal lineages on human phenotypes in Oceania. The few genetic studies undertaken emphasize the uniqueness and antiquity of Indigenous Australian genomes, with possibly the largest proportion of Denisovan ancestry of any population in the world. In this review, we focus on the potential contributions of ancient genes/pathways to modern human phenotypes, while also highlighting the evolutionary roles of genetic adaptation to dietary and environmental changes associated with an adopted Western lifestyle. We discuss the role of genetic and epigenetic factors in the pathogenesis of T2D in understudied Indigenous Australians, including the potential impact of archaic gene lineages on this disease. Finally, we propose that greater understanding of the underlying genetic predisposition may contribute to the clinical efficacy of diabetes management in Indigenous Australians. We suggest that improved identification of T2D risk variants in Oceania is needed. Such studies promise to clarify how genetic and phenotypic differences vary between populations and, crucially, provide novel targets for personalised medical therapies in currently marginalized groups.

Keywords Archaic human genes · Genome-wide association studies · Obesity · Diabetes mellitus · Indigenous Australians

1 Introduction

The prevalence of diabetes mellitus (DM) has increased exponentially worldwide and is currently the seventh leading cause of death. Type 2 diabetes mellitus (T2D) in particular has reached global epidemic proportions posing a significant challenge for public healthcare systems [1, 2]. Although obesity and sedentary lifestyle are strong and modifiable risk factors for T2D, some human populations seem to be particularly affected, suggesting a sizable genetic component [2]. Aboriginal Australians and Torres Strait Islanders experience disproportionately high levels of diabetes; it has been estimated that they are three to five times more likely to develop T2D than Australians of European descent [3]. Notably, Aboriginal and Torres Strait Islander children are eight times more likely to develop T2D than their non-indigenous peers [2].

Indigenous Australians are diagnosed with diabetes approximately 14 years earlier than European patients [4]. Moreover, Aboriginal Australians and Torres Strait Islanders also have poor clinical outcomes from diabetes treatment with six-fold increased mortality rates compared to non-indigenous Australians, with T2D being the leading cause of death [2]. Importantly, many strategies and treatment regimens targeting this health disparity experienced by Aboriginal peoples have had limited impact on disease prevention. Furthermore, the implemented interventions to improve the healthcare for Aboriginal Australians are often not sustainable [5].

✉ Malgorzata Monika Brzozowska
m.brzozowska@garvan.org.au

1 Endocrinology Department, Sutherland Hospital, Sydney, New South Wales, Australia

2 St George & Sutherland Hospital Clinical School, University of New South Wales, Sydney, Australia

3 School of Life and Environmental Sciences, Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia

4 The Palaeogenomics and Bio-Archaeology Research Network, Research Laboratory for Archaeology and History of Art, University of Oxford, Oxford, UK

5 Statistics and Bioinformatics Group, School of Fundamental Sciences, Massey University, Palmerston North 4410, New Zealand

In this review, we discuss studies of DNA variants that influence predisposition to obesity and T2D in Indigenous Australians, including the potential impact of archaic human lineages on these diseases. We review the significance of genome-wide association studies in Aboriginal groups, including possible evolutionary roles of genetic selection associated with an adopted Western lifestyle (Fig. 1). Major topic areas and key studies discussed in our review are highlighted in Table 1.

2 Indo-Pacific human populations, including indigenous Australians, are genomically understudied

Genome-wide association studies (GWAS) have uncovered significant links between specific genetic variants and modern diseases, including differences in biological trait distributions across populations. Importantly, GWAS findings have facilitated a deeper understanding of biological mechanisms, population genetics and the evolutionary context of complex diseases such as diabetes mellitus. However, it has been only recently that advances in DNA technologies have allowed us to study the intersections between large-scale genomic data, archaic hominin lineages and modern epidemiology. A recent analysis of 2,511 genomic studies with 35 million samples showed that the majority of participants were of European ancestry (81%), with the remainder mostly of Asian descent (14%) [10]. In particular, due to the complex combination of historical, cultural, scientific and logistical factors, there is an extreme paucity of genomic data from the Indo-Pacific region, including Indigenous Australians. Pacific Islanders represent only 0.28% of genomic samples studied, with Native Americans and Australian Aboriginal participants contributing a mere 0.05%.

Fig. 1 Role of genetics, epigenetics and environmental risk factors in type 2 diabetes in Indigenous Australians

Table 1 Summary of main topic areas and key studies or reviews

Topic	Study (reference)
Indigenous Australians and T2D*	Davis et al. [4]
	Zimmet et al. [2]
Understudied genomics of Indo-Pacific human populations, including Indigenous Australians	Reich et al. [6]
	Reich et al. [7]
	Sankararaman et al. [8]
	Sankararaman et al. [9]
	Popejoy et al. [10]
	Sankararaman et al. [11]
	Simonti et al. [12]
	Tobler et al. [13]
	Jacobs et al. [14]
Impact of archaic genomes on modern humans	T2D Consortium et al. [15]
	Vernot et al. [16]
	Gibbons et al. [17]
	Simonti et al. [12]
Overview of genetic factors in the pathogenesis of T2D in Aboriginal populations	Busfield et al. [18]
	Daniel et al. [19]
	O'Dea et al. [20]
	Anderson et al. [21]
	McCoy et al. [22]
Genetic adaptation to dietary and environmental changes	Williams et al. [23]
	Neel [24]
	Cordain et al. [25]
	Xu et al. [26]
	Prentice et al. [27]
	Dabelea et al. [28]
	Heijmans et al. [29]
	Prentice et al. [30]
	Speakman [31]
	Ayub et al. [32]
	Chamberlain et al. [33]
	Chamberlain et al. [34]
	Ruhli et al. [35]
	Wang et al. [36]
	Xue et al. [37]
	Titmuss et al. [38]

*T2D – type 2 diabetes mellitus

Furthermore, the number of indigenous participants in GWAS studies has actually declined since 2009 [10].

The importance of studying genomic variation in underrepresented populations is driven by the need to discover population-specific differences in the frequency of presumed disease-causing genetic variants, as well as to examine new genetic associations with the disease traits. Moreover, identifying differences in risk alleles for common complex diseases across human populations will advance our understanding of genetic impacts on disease risk, with concomitant improvements in disease prevention strategies and treatments.

Interestingly, a number of genetic studies link predisposition to diabetes mellitus and other diseases to variants acquired from historical interbreeding of modern humans with archaic human species, such as Neanderthals and Denisovans [12, 15]. The Neanderthal–Denisovan lineage split from *Homo sapiens* approximately 744,000 years ago and these two archaic groups diverged from each other approximately 200,000 years later [39]. Comparisons of DNA sequences, introgressed from Neanderthals in present-day humans, have estimated that admixture with Neanderthals occurred 37,000–86,000 years before the present and most likely between 47,000 and

65,000 years ago [8]. Admixture with Denisovans first took place within a similar time span, approximately 44,000–55,000 years ago [11]. Denisovans share a deep, but common, ancestral population with Neanderthals. Due to shared ancestral alleles [40], it may therefore sometimes be difficult to distinguish between Neanderthal and Denisovan admixture as these two archaic linages are on average more similar to each other than either is to modern humans [6, 41]. Genomes of modern Eurasians contain a small fraction (~1.5–4%) of DNA originating from Neanderthals [42] with low amounts of Denisovan ancestry (0.2%) being found in East Asia [43]. However, rates of archaic lineages in Pacific peoples, including Indigenous Australians, are markedly higher (3–6%) [7]. Moreover, recent research identified high-confidence archaic haplotypes in inhabitants from Island Southeast Asia and New Guinea from two divergent Denisovan lineages, with the latest introgression events perhaps occurring much more recently than in other parts of the world [14]. Importantly, introgressed alleles that find themselves within a new genetic background frequently have negative fitness effects with negative selection likely affecting multiple, weakly deleterious alleles of Neanderthal ancestry [41]. The strength of selection against Neanderthal DNA in modern humans is dependent on the gene density of selected sites and their recombination rate [44, 45]. Despite a general trend towards negative selection against introgressed Neanderthal alleles, certain genomic regions may have degrees of Neanderthal ancestry as high as 64% in Europeans and 62% in Asians, indicating positive selection on these specific regions [9]. Similar patterns are expected to hold for Denisovan ancestry.

Interestingly, recent analyses of genome-wide genetic data from populations including South Asia, Southeast Asia and Oceania, suggested that archaic Denisovans lived over a broad geographic range from Siberia to tropical Asia [7]. Congruently, genetic studies on Aboriginal Australians, though limited, have demonstrated both the uniqueness and antiquity of Aboriginal Australian genomes including strong evidence of Denisovan genetic material, possibly at the highest rate in the world [7]. As much as 4% of indigenous Australian nuclear genomes may also come from an ancient hominin lineage that is yet to be identified [46]. In line with these studies, Indigenous Papuan and Australian people derive 3–6% of their DNA from Denisovans, with an increase in allele sharing between Denisovans and Aboriginal Australians compared to other Eurasians and Africans [6, 7, 47]. Furthermore, in Oceanians (such as the negrito Mamanwa of the Philippines, Indigenous Australians and Papuans from New Guinea), the average length of Denisovan fragments is longer than Neanderthal fragments, implying a more recent average date of Denisovan admixture in the history of these populations [11]. Moreover, in Oceanians the decline of introgressed Denisovan ancestry is estimated to be slower than the rate at sites informative of Neanderthal ancestry [11]. This could be due to multiple distinct Denisovan introgressions or that some introgressed Denisovan variants are not under the same level of negative selection [11]. A key take-home message, however, is that there is extremely limited literature examining the impact of Denisovan or Neanderthal lineages on human phenotypes in Oceania, with a striking overrepresentation of genomic studies on European populations.

3 Impact of archaic genomes on modern humans

A recent study that analysed the contribution of common Neanderthal variants to over 1,000 electronic health record (EHR)-derived phenotypes in ~28,000 adults of European ancestry, reported that archaic admixture continues to influence disease risk in modern humans [12]. These analyses confirmed the impact of Neanderthal DNA on neurological, psychiatric, immunological and dermatological modern human phenotypes. Importantly, it was found that many alleles associated with complex diseases such as systemic lupus erythematosus, primary biliary cirrhosis, Crohn's disease and T2D have been introgressed from Neanderthals into non-African modern humans [16]. Congruently, Denisovan admixture in Indigenous Australians, the largest in the world, might have contributed to overrepresentation of archaic disease risk alleles in Indigenous Australians in comparison with any other populations.

In particular, the presence of Neanderthal alleles explained a significant percent of the risk for a number of medical conditions including actinic and seborrheic keratosis, obesity and mood disorders including depression [12, 17]. In addition, Neanderthal haplotypes have been shown to influence hypercoagulable state, thiamine metabolism, urinary tract disorders and nicotine addiction [17]. Neanderthal-introgressed haplotypes may have also affected the expression levels of multiple genes including risk alleles for celiac disease in the chemokine receptor (CCR) gene family, which was possibly maintained by adaptive forces in early European modern human populations [48]. Moreover, variants within this Neanderthal-derived haplotype have been associated with severity of malaria [49]. Another example is a nonsynonymous variant of the *ZNF365D* gene present in ~32% of Europeans and absent from Africans, which was inherited from Neanderthals and is associated with a higher risk of Crohn's disease and susceptibility towards human uric acid nephrolithiasis [9, 50, 51].

Limited research has proposed that increased rates of obesity and T2D in Europeans and Asians compared to Africans are in part due to interbreeding with ancient Neanderthals [9], while Denisovan admixture has affected activity of phospholipid transporter genes and fat metabolism [11]. The genetic analysis, which examined 9.2 million single nucleotide polymorphisms (SNPs) in Mexican and Latin American populations in 3,848 people with T2D and 4,366 non-diabetic

controls, identified the monocarboxylate transporter *SLC16A11* as a novel candidate gene [15]. Notably, the *SLC16A11* haplotype was present in approximately half of Native American samples, and in approximately 10% of East Asians, while being rare or absent in samples from Europe and Africa. Subsequent analysis of an archaic unpublished genome of a Neanderthal from Denisova cave reported the presence of one silent and four missense SNPs in the *SLC16A11* gene indicating that the observed *SLC16A11* haplotype (referred to as the "5 SNP" haplotype) has entered into modern humans from Neanderthals [15]. This Neanderthal sequence was nearly identical to those present in 1000 genomes from modern Native Americans who were homozygous for the 5 SNP haplotype [15]. The presence of the 5 SNP haplotype significantly increases the prevalence of T2D, by up to 29%, in individuals with Native American ancestry [15]. Notably, people affected by the 5 SNP of the *SLC16A11* haplotype develop T2D at a younger age and with a lower BMI than non-carriers. The researchers proposed that *SLC16A11* may influence predisposition to diabetes through its effects on hepatic lipid metabolism affecting intracellular triacylglycerol levels.

Other studies suggest that some archaic alleles may have been under positive selection. Specific Neanderthal alleles appear to have resulted in a selective advantage for their modern European carriers through their impact on lipid catabolism [52]. Introgression of ancient alleles from Neanderthals and Denisovans to the modern human gene pool might have also conferred a substantial immune advantage the modern humans. A recent report described a cluster of three Toll-like receptors (*TLR6-TLR1-TLR10*), present in modern Asians and Europeans, who acquired these advantageous alleles through admixture with archaic humans [53]. Furthermore, these introgressed alleles of immunity genes continue to have functional effects in modern humans. The archaic-like alleles underlie differences in the expression of the *Toll-like receptor* (*TLR*) genes, and are essential for eliciting inflammatory and antimicrobial responses and for activating an adaptive immune response. Archaic immunity genes have also been implicated in increased hypersensitivity to non-pathogenic allergens, resulting in allergic diseases in present-day people [54]. Interestingly, a recent study proposed the increased expression of *TLR4* as a possible mediator of pancreatic islet inflammation [55] and as a risk factor for T2D independent of gender, blood glucose concentrations and body mass index (BMI) [56].

4 Overview of genetic factors in the pathogenesis of T2D in aboriginal populations

The differences in prevalence of diabetes mellitus, clinical complications and mortality rates between Indigenous and non-indigenous Australians represent a complex interplay between genetic susceptibility and environmental and lifestyle risk factors. In particular, obesity and age (35 years and onwards) are two critical risk factors affecting the prevalence of T2D in Aboriginal populations [20]. Indigenous Australians display body habitus which differs from non-indigenous Australians with preferential abdominal fat deposition, exacerbating their insulin resistance [57] and leading to a higher risk of diabetes mellitus with BMI scores above 22 kg/m^2.

Recent GWAS studies on individuals with primarily European ancestry have mapped approximately 100 independent SNPs that modulate the risk of T2D and glycaemic related traits [19, 58, 59]. Despite strong epidemiologic evidence implicating genetic factors in the pathogenesis of T2D in Aboriginal populations, there is a notable paucity of data in the literature reporting diabetes-susceptibility genes in Indigenous Australians. The first full-genome linkage analysis conducted in Indigenous Australians from North Stradbroke Island, Queensland, was published in 2002, and identified three distinct regions of genetic linkage to T2D [18]. Multipoint linkage analysis identified evidence for a T2D susceptibility allele at chromosome position 2q24.3, previously implicated in the aetiology of T2D in other ethnic groups [60]. Candidate genes at this locus include a gene encoding the *growth-receptor-binding protein 14* (*GRB14*), which is a negative regulator of insulin signalling [61], as well as a gene encoding the *islet-specific glucose-6-phosphate catalytic subunit–related protein*. Raised glucose-6-phosphatase activity has been shown to reduce glucose induced insulin secretion in an obese-hyperglycaemic ob/ob mouse model of T2D [62]. The analysis also pointed to the presence of diabetes susceptibility loci on chromosomes 3q29 and 8p22, which have been previously linked with an increased risk for diabetes mellitus in other populations [60, 63]. Candidate genes in these regions include *lipoprotein lipase* (*LPL*), previously associated with insulin resistance in Mexican Americans [63], and *type 1 protein phosphatase inhibitor 2* (*PPR12*), which constitutes a key component of the insulin signalling pathway through the regulation of glycogen metabolism [64].

The recent analysis of genetic markers in 402 individuals from a Western Australian Aboriginal community, including 89 patients with T2D, has identified novel DNA variants in previously reported major metabolic pathways that influence predisposition towards obesity and T2D [21]. Of these 89 individuals affected by T2D, 65 were of unadmixed Martu ancestry (an Indigenous Australian people, who are part of the Western Desert cultural block) and 24 individuals of mixed ethnicity. Although none of the identified SNPs achieved genome-wide significance, likely due to the small sample size, the SNP analysis identified multiple risk genes for BMI and T2D, with many in known candidate genes

identified in previous studies on other ethnic groups. The top hit was *neurotrophic receptor tyrosine kinase 2* (*NTRK2*), which regulates eating behaviour and energy homeostasis via *melanocortin-4 receptor* (*MC4R*). Interestingly, *MCR4* was also found as a candidate gene in this study, and although an association of *NTRK2* with T2D has not been previously reported, *MCR4* is a well-known risk gene for high BMI [65–67]. Another top candidate gene identified by this study was *insulin-like growth factor 2 mRNA-binding protein 2* (*IGF2BP2*), which has also been previously identified as a T2D susceptibility gene in other ethnic groups [68–70].

This analysis has provided stronger evidence for an association between Indigenous BMI and SNPs that lie in the intergenic region between *SLC28A3* and *NTRK2* on chromosome 9q21.33, as well as with *PIK3C2G*, a gene linked with T2D and low serum insulin levels in Japan [71], and *CNTNAP2* [72], a gene required for proper localization of the potassium voltage-gated channel *KCNA1,* although both to a lesser degree.

Furthermore, the results from the Aboriginal genome analysis identified *BCL9* as a novel diabetes risk gene. BCL9, a transcription coactivator, modulates the function of the WNT-signalling pathway [73], which is known to be involved in the development of T2D [74]. Moreover, this first genome-wide analysis in an Australian Aboriginal population identified *KCNJ6, KCNA1*, and *GABRR1*, all involved in regulating pancreatic function, as diabetes susceptibility genes among Indigenous Australians.

Taken together, these results from the first GWAS performed on Indigenous Australians did not point to susceptibility genes that can by themselves explain the disproportionally high risk of T2D in Aboriginal populations. Notably, recent genomic analysis indicated that Aboriginal Australians first diverged from Eurasian populations approximately 50,000 years ago and, as highlighted above, subsequently admixed with multiple archaic populations including Denisovans and Neanderthals [46]. As Oceanians have the largest frequency of Denisovan admixture in the world, such archaic lineages might be expected to have more effect on Australians than on other populations, especially as Neanderthal-inherited sequences continue to have measurable impacts on gene expression that contribute to variation in modern human phenotypes elsewhere [22].

Although the limitation of the first GWAS study in Australian Aboriginals was its small sample size with subsequently limited power, we hope that the results from this pioneering study will stimulate replication studies in other Indigenous Australian groups with the key goal of improving healthcare outcomes. Furthermore, future identification of risk variants for T2D in Indigenous Australians may need to consider genetic admixture from archaic populations [13], recently implicated in the pathogenesis of diabetes in Mexican and Latino Americans [15].

5 Genetic adaptation to dietary and environmental changes

Changes in food availability and diet composition may have also significantly influenced the metabolic health of Indigenous Australians. Before the recent arrival of Europeans, for thousands of years, Aboriginal people lived as hunter-gatherers with a high reliance on animal-based foods coupled with the relatively low (by Western modern standards) carbohydrate content of wild plant foods. Modern reconstructions of worldwide hunter-gatherer diets have revealed their very high protein content from which indigenous people derive between 19 and 50% of their total energy supply [25]. In contrast, modern diets provide on average more than 70% of energy intake from refined sugars, refined vegetable oils, highly processed cereals and dairy products [75]. The evolutionary mismatch between modern dietary constituents and the food available prior to the agricultural revolution has been considered a major factor in the obesity epidemic [76].

In contrast to the relatively slow changes in the composition of modern diets for the European population, including the increase of carbohydrates associated with the agricultural transition, a fast and very recent introduction of modern diets may have been deleterious to the metabolic health of Aboriginal populations. The concept of 'limited opportunity' for genetic adaptation towards these new environmental factors in Australian Aboriginal populations has also been supported by the observation that the presence of European HLA haplotypes in Indigenous Australians is protective against obesity [23]. Proposed mechanisms for the evolutionary origins of the current obesity epidemic among Indigenous Australians include the 'thrifty gene' hypothesis [24, 30] and epigenetic factors, particularly in conjunction with the loss of traditional lifestyles and associated changes to a Western diet. The physiological system that once encouraged survival in times of famine may thus now be contributing to obesity with excess calories being stored as energy-rich fat to combat potential times of scarce resources [77, 78]. Furthermore, the presence of 'thrifty genes' might have conferred a significant reproductive advantage as fertility and the chances of successful pregnancy diminish once the body fat mass falls below a critical threshold [79]. Alternatively, modern environmental exposure may be exacerbating the effects of candidate genes, with genotypic effect sizes being larger than those seen in other populations. It is, however, important to point out that there is a lack of compelling evidence for gene-gene and gene-environment interactions in multifactorial diseases [80], possibly a corollary methodological challenges in human observational studies being marred by variability in study designs and exposure to measurement error [81]. Therefore, alternative hypotheses have been proposed to explain the heterogeneity of diabetes and obesity between and within populations [31]. A modified 'thrifty genes hypothesis' suggested that

only agricultural societies experienced food scarcity during cyclical famine with sufficient pressure to select for thrifty genes [27]. Furthermore, given the recent advent of agriculture (approximately 10,000 years ago), most polymorphisms causing obesity have had insufficient time to move towards fixation [30]. Recent introduction to a diabetogenic diet negatively affected metabolic health in Native Americans and Pacific Islanders, while Europeans were pioneer farmers and appear to have become partially adapted to the diet through longer-term natural selection [82]. Notably, a temporary reversion to a traditional hunter-gatherer lifestyle among a group of Indigenous Australian adults resulted in significant improvements in cardio-metabolic risk profiles related to diabetes mellitus [83].

The challenges associated with the 'thrifty genes hypothesis' have been extrapolated to the potential role of intrauterine undernutrition with future increased risk for metabolic disorders in the developing foetus. Poor foetal growth due to undernutrition during pregnancy has been associated with future risk of T2D through the underdevelopment of foetal pancreatic beta cells, increased peripheral insulin resistance, and subsequent hyperglycemia due to increased adipose tissue deposition [84]. Finally, a genetic drift hypothesis proposed that obesity is a consequence of random mutation and drift in genes that regulate the upper limits of body weight control and that obesity predisposing alleles are selectively neutral [31]. Notably, the findings from an analysis of 65 loci associated with susceptibility to T2D mellitus in samples of African, European and East Asian ancestry failed to find evidence in support of the thrifty gene hypothesis [32], congruent with studies that considered T2D as being neutral from an evolutionary perspective [85, 86] because it largely presents in post-reproductive ages. It is important, however, to point out that T2D has polygenic inheritance with both rare and common genetic traits contributing to the effects of individual risk variants. Furthermore, the findings from a meta-analysis of genome-wide association studies identified that the rarer genetic variants tend to have larger effects on T2D risk and are more likely to be at low frequencies in the population due to negative selection [37]. Other recent analysis further challenged the 'thrifty genes hypothesis' with little evidence for positive selection at SNPs linked to BMI, combined with selection favouring leanness at some alleles, thus disputing the suggestion that obesity provided a selective advantage to survive famines, or any other selective advantage [36].

The identification of genetic loci with a major role in modifying dietary behavior in modern humans has largely been limited to genes associated with energy metabolism pathways, including carbohydrate digestive enzymes. A well-known example is the genetic basis of lactase persistence, encoded by the gene for the lactase enzyme (*LCT)* that breaks down milk-sugar lactose. The production of lactase declines after weaning in all mammals including humans [87]. However, some humans are lactase persistent, a trait that is particularly common in some parts of the world, for example Northern Europe and Eastern Africa [88, 89]. Lactase persistence evolved in cultures where dairy products are consumed in high quantities, typically pastoral cultures. The current models trace the mutation associated with the lactase persistence trait back to the time of animal domestication [90–93]. Another interesting example of the evolution of metabolic enzymes in humans is the positive selection on salivary amylase *(AMY1)* gene copy number, which correlates positively with human populations that have historically favored a high-starch diet [94]. Whereas the Neanderthals had only one copy of *AMY1*, over 98% of modern humans carry multiple copies of the gene [43, 94, 95]. In addition to the *LCT* and *AMY1* genes, many other enzymes may be important in dietary adaptations. The *NAT2* gene encodes the drug metabolizing enzyme *N-acetyltransferase 2*, which has been shown to be a possible target of selective pressures associated with the agricultural transition [96]. Other genes involved in metabolism also carry signals of selection in genome-wide studies, thus raising the possibility that most of the selection identified in these studies coincide with the transition to agriculture and animal farming [97].

Another candidate gene possibly responsible for the adaption to modern diets is *NTRK2*, *a neurotrophic receptor tyrosine kinase 2*, which has been shown to regulate mammalian eating behaviour and energy balance downstream of the melanocortin-4 receptor (*MC4R*) through the brain-derived neurotrophic factor *BDNF* [26, 98]. The NTRK2 protein has previously been established to regulate BMI, and a mutation in *NRTK2* has been identified in patients with severe obesity [99] as well as being linked with mood disorders [100]. Interestingly, the regulatory regions of *NTRK2* lie in a genetic region that has been shown to be influenced by so-called 'positive selective sweeps' that took place after the last admixture between Denisovans, Neanderthals and modern humans [22, 101]. These areas, suggested to have been under positive selection, are characterized by unusually long and high frequency genomic regions with low genetic diversity. These ancient stretches have been proposed to have reached fixation faster than what is expected under neutral evolution [91]. One explanation could be that these positive selective sweeps have been unusually strong and not allowing enough time for recombination to occur, thereby leading to a fixation of a whole genetic region [101]. Therefore, although there is no unequivocal evidence to support the hypothesis that the Neanderthal haplotype-tagging SNPs in *NTRK2* are associated with obesity in Indigenous Australians, such a hypothesis is compelling. Further studies are required to test the hypothesis that positive selective sweeps have occurred in human genes such as *NTRK2*, and these are particularly needed to advance the molecular understanding of obesity related pathways in Australia's Indigenous communities.

It can be argued that short-term changes in body height and body weight are not the result of changes in gene frequencies, but simply adaptive, non-heritable responses to changing living conditions and the ability of the human body to respond to such changes is a product of its earlier evolution [102]. The vast majority of mutations that occur are either neutral with respect to fitness (defined as the individual's ability to survive and reproduce) or are disadvantageous. If they are disadvantageous, they will tend to be removed from the population because their bearers will be less likely to survive and/or reproduce (negative selection). Occasionally, a new mutation confers a selective advantage and increases the fitness of individuals bearing it (positive selection), so that it will eventually reach fixation. Changes in gene frequencies by natural selection are determined by differences in fertility and mortality over generations, which ultimately determine the fitness of a particular population in a given environment [103, 104].

A recent analysis of 118 countries found a negative correlation between natural selection as measured by a 'Biological State Index' and the incidence of diabetes mellitus [35]. The Biological State Index of a given population represents the likelihood of an individual passing their genes to the next generation [105]. The lower the ratio, the less opportunity for selection [35]. Interestingly, in that study, the relationship between the prevalence of diabetes mellitus and reduced natural selection, after controlling for income and urbanization, was stronger for type 1 diabetes mellitus (T1D) ($R^2 = 0.55$) than for T2D ($R^2 = 0.13$) [35]. Such a result could be partly explained by an improvement in life expectancy, through effective insulin treatment effectively negating the genetic susceptibility to type 1 and, to a lesser extent, type 2 diabetes.

Although T2D mellitus is overrepresented in Aboriginal Australians, recent data reveal a similar incidence rate of T1D among Aboriginal and Torres Strait Islander people and non-indigenous Australians [106]. T1D is a chronic immune-mediated disease-causing attrition and death of the insulin-producing pancreatic β cells, resulting in a life-long requirement for exogenous insulin. T1D is recognized to have a multi-factorial pathogenesis, in which both genetic and environmental factors play important roles [107]. Today, >60 loci associated with T1D have been identified, with human leukocyte antigen (HLA) association being the strongest [108]. In most countries, the incidence of T1D is increasing by ~3–4% every year, most notably in children and adolescents likely due to earlier and greater affordability of insulin and improved healthcare. In the Ruhli et al. study [35], there was a stronger, positive association between the Biological State Index and the prevalence of T1D in regions where insulin was available earlier due to improved access to health services. In Australia, life expectancy at birth for people with T1D has been estimated to be about 12 years less than the general Australian population [109]. These results are comparable with a Scottish study, which indicated an estimated loss of life expectancy at age 20 of approximately 11 years for men and 13 years for women compared to the general population without T1D [110]. In most countries [109], patients with T1D have fewer children than their unaffected siblings. This effect is more evident in women and in older birth cohorts. Onset of T1D as an adult rather than a child is associated with a higher number of offspring, even after accounting for birth cohort and disease duration [111]. These data are suggestive of lower fitness (reproductive success) of individuals with early T1D compared with individuals with T2D in the modern environment. Therefore, a better understanding of genetic and environmental mechanisms of T1D has strong potential to contribute to novel, more effective treatment strategies for this chronic medical disorder.

Environmental factors such as age, obesity, physical activity and diet have a crucial role in the development of obesity and T2DM. These factors may change patterns of gene expression via epigenetic mechanisms, including DNA methylation, histone modification and microRNA regulation. DNA methylation, the addition of a methyl group at the fifth position of the cytosine ring, is an important molecular mechanism of epigenetic modification [112]. Furthermore, DNA sequence variations such as CpG-SNP, structural variations and gene–gene interactions can also modulate epigenetic regulation.

The epigenetic contribution to obesity and diabetes has been extensively studied in animal models including non-human primates and to a much lesser degree in human studies. Limited observational studies reported that obesity and related phenotypes induce epigenetic dysregulation with altered methylation patterns in humans with T2D compared with non-diabetic controls. Together, these studies support a link between BMI and epigenetic variation of candidate genes for both obesity and T2D, which seems to affect gene expression and metabolism. The reader is referred to a recent review summarising epigenetic impacts on important target tissues in humans that contribute to deranged metabolism including pancreatic islets, adipose tissue and skeletal muscle [113].

Growing evidence indicates that, apart from obesity, several epigenetic risk factors, including the unfavourable environment of hyperglycemia and insulin resistance during intrauterine development, may contribute to increasing diabetes rates in Indigenous young people [38, 114]. Strong epidemiological data link human prenatal exposure to famine with persistent epigenetic differences, as well as increased risk of disease later in life [29, 115]. Indigenous Australians have a high prevalence of gestational diabetes (GDM) [33]. Moreover, they face a fourfold risk of developing type 2 diabetes after pregnancies complicated by GDM in comparison with non-indigenous women [34], thus triggering an increased transgenerational risk of metabolic disease. The uterine environment of hyperglycemia and insulin resistance may induce changes in DNA methylation with subsequent lifelong metabolic risk possibly

influenced by this timing of exposure [116]. Such a relationship between changes in DNA methylation and impaired metabolic homeostasis has been observed among the Pima Indian peoples of Arizona. Their children, who were exposed to intrauterine hyperglycaemia, had a 3.7-fold higher risk of type 2 diabetes with higher body mass index compared to siblings who were born before the mother developed diabetes, suggesting an even greater contribution of the intrauterine environment than underlying genetic susceptibility [114]. Intrauterine exposure to maternal diabetes and obesity may contribute to up to 47% of T2D in youth, with affected children developing metabolic disease earlier than the preceding generation [28].

Clearly future large-scale genomic studies and studies specifically addressing environmental risk factors are required to improve our understanding of the biological mechanisms underlying T2D and other common metabolic diseases, and this is especially true for severely understudied Indigenous Australian communities.

6 Conclusions

Indigenous Australians are disproportionately affected by T2D compared to non-indigenous Australians. This is likely due to a complex interplay between acquired and inherited risk factors. As current medical interventions are having only a modest effect in alleviating the burden of this potentially preventable condition, more DNA based studies are needed to allow for improved personalized therapies in Aboriginal populations. Furthermore, considering the recent evidence of the impact of archaic genetic admixture, the possibility that an archaic legacy has contributed to an increased diabetes risk among Indigenous populations requires serious consideration. The functional consequences of introgressed variation in populations with other than European ancestry include a recently identified Neanderthal-introgressed *SLC16A11* haplotype, which explains ~20% of the increased T2D prevalence in Mexican and Latin American populations [15]. Furthermore, future therapeutic interventions aimed to increase SLC16A11 levels or activity may enhance the efficacy of therapy for T2D. The technical advances in whole-genome sequencing, functional genomics and population genetic modelling will increase our knowledge of evolutionary processes that have contributed to human adaptation, complex diseases and survival over time. Further genetic studies are now required to identify the pathways inherited from archaic human genomes, which may advance our understanding of phenotypic differences between populations and, crucially, provide novel targets for medical therapies in currently marginalized Indigenous groups.

Acknowledgements We acknowledge the Bedegal and Gadigal peoples, the Traditional Custodians of the lands of the University of New South Wales and the University of Sydney, and we pay our respects to Elders past, present and future, both Bedegal, Gadigal and all Indigenous groups across Australia. We acknowledge the "structural nature of our problem", as put forth in the Statement from the Heart. Just as Indigenous lands have always been a learning space for Aboriginal nations, one of the oldest knowledge systems in the world, we offer our knowledge from a western science perspective as a shared path to redressing past and ongoing healthcare wrongs.

Compliance with ethical standards

Conflict of interest There are no supporting grants or conflicts of interest to declare.

References

1. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018;41(5):963–70.
2. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol. 2014;2(1):56–64.
3. Hoy WE, Kondalsamy-Chennakesavan S, Wang Z, Briganti E, Shaw J, Polkinghorne K, et al. Quantifying the excess risk for proteinuria, hypertension and diabetes in Australian Aborigines: comparison of profiles in three remote communities in the Northern Territory with those in the AusDiab study. Aust N Z J Public Health. 2007;31(2):177–83.
4. Davis TM, McAullay D, Davis WA, Bruce DG. Characteristics and outcome of type 2 diabetes in urban Aboriginal people: the Fremantle Diabetes Study. Intern Med J. 2007;37(1):59–63.
5. Demaio A, Drysdale M, de Courten M. Appropriate health promotion for Australian Aboriginal and Torres Strait Islander communities: crucial for closing the gap. Glob Health Promot. 2012;19(2):58–62.
6. Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, et al. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature. 2010;468(7327):1053–60.
7. Reich D, Patterson N, Kircher M, Delfin F, Nandineni MR, Pugach I, et al. Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. Am J Hum Genet. 2011;89(4):516–28.
8. Sankararaman S, Patterson N, Li H, Paabo S, Reich D. The date of interbreeding between Neandertals and modern humans. PLoS Genet. 2012;8(10):e1002947.
9. Sankararaman S, Mallick S, Dannemann M, Prufer K, Kelso J, Paabo S, et al. The genomic landscape of Neanderthal ancestry in present-day humans. Nature. 2014;507(7492):354–7.
10. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538(7624):161–4.
11. Sankararaman S, Mallick S, Patterson N, Reich D. The Combined Landscape of Denisovan and Neanderthal Ancestry in Present-Day Humans. Curr Biol. 2016;26(9):1241–7.
12. Simonti CN, Vernot B, Bastarache L, Bottinger E, Carrell DS, Chisholm RL, et al. The phenotypic legacy of admixture between modern humans and Neandertals. Science. 2016;351(6274):737–41.
13. Tobler R, Rohrlach A, Soubrier J, Bover P, Llamas B, Tuke J, et al. Aboriginal mitogenomes reveal 50,000 years of regionalism in Australia. Nature. 2017;544(7649):180–4.

14. Jacobs GS, Hudjashov G, Saag L, Kusuma P, Darusallam CC, Lawson DJ, et al. Multiple Deeply Divergent Denisovan Ancestries in Papuans. Cell. 2019;177(4):1010–21e32.
15. Consortium STD, Williams AL, Jacobs SB, Moreno-Macias H, Huerta-Chagoya A, Churchhouse C, et al. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. Nature. 2014;506(7486):97–101.
16. Vernot B, Akey JM. Resurrecting surviving Neandertal lineages from modern human genomes. Science. 2014;343(6174):1017–21.
17. Gibbons A. Human Evolution Neandertal genes linked to modern diseases. Science. 2016;351(6274):648–9.
18. Busfield F, Duffy DL, Kesting JB, Walker SM, Lovelock PK, Good D, et al. A genomewide search for type 2 diabetes-susceptibility genes in indigenous Australians. Am J Hum Genet. 2002;70(2):349–57.
19. Daniel M, Rowley KG, McDermott R, O'Dea K. Diabetes and impaired glucose tolerance in Aboriginal Australians: prevalence and risk. Diabetes Res Clin Pract. 2002;57(1):23–33.
20. O'Dea K, Rowley KG, Brown A. Diabetes in Indigenous Australians: possible ways forward. The MJA. 2007;186(10):494–5.
21. Anderson D, Cordell HJ, Fakiola M, Francis RW, Syn G, Scaman ES, et al. First genome-wide association study in an Australian aboriginal population provides insights into genetic risk factors for body mass index and type 2 diabetes. PLoS One. 2015;10(3):e0119333.
22. McCoy RC, Wakefield J, Akey JM. Impacts of Neanderthal-Introgressed Sequences on the Landscape of Human Gene Expression. Cell. 2017;168(5):916–27 e12.
23. Williams DR, Moffitt PS, Fisher JS, Bashir HV. Diabetes and glucose tolerance in New South Wales coastal Aborigines: possible effects of non-Aboriginal genetic admixture. Diabetologia. 1987;30(2):72–7.
24. Neel JV. The "thrifty genotype" in 1998. Nutr Rev. 1999;57(5 Pt 2):S2–9.
25. Cordain L, Miller JB, Eaton SB, Mann N, Holt SH, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr. 2000;71(3):682–92.
26. Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, Jones KR, et al. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. Nat Neurosci. 2003;6(7):736–42.
27. Prentice AM. Early influences on human energy regulation: thrifty genotypes and thrifty phenotypes. Physiol Behav. 2005;86(5):640–5.
28. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D'Agostino RB Jr, Liese AD, Vehik KS, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care. 2008;31(7):1422–6.
29. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008;105(44):17046–9.
30. 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. 2008;32(11):1607–10.
31. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. Int J Obes. 2008;32(11):1611–7.
32. Ayub Q, Moutsianas L, Chen Y, Panoutsopoulou K, Colonna V, Pagani L, et al. Revisiting the thrifty gene hypothesis via 65 loci associated with susceptibility to type 2 diabetes. Am J Hum Genet. 2014;94(2):176–85.
33. Chamberlain C, Banks E, Joshy G, Diouf I, Oats JJ, Gubhaju L, et al. Prevalence of gestational diabetes mellitus among Indigenous women and comparison with non-Indigenous Australian women: 1990–2009. Aust N Z J Obstet Gynaecol. 2014;54(5):433–40.
34. Chamberlain CR, Oldenburg B, Wilson AN, Eades SJ, O'Dea K, Oats JJ, et al. Type 2 diabetes after gestational diabetes: greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. Diabetes Metab Res Rev. 2016;32(2):217–27.
35. Ruhli F, van Schaik K, Henneberg M. Evolutionary Medicine: The Ongoing Evolution of Human Physiology and Metabolism. Physiology (Bethesda). 2016;31(6):392–7.
36. Wang G, Speakman JR. Analysis of Positive Selection at Single Nucleotide Polymorphisms Associated with Body Mass Index Does Not Support the "Thrifty Gene" Hypothesis. Cell Metab. 2016;24(4):531–41.
37. Xue A, Wu Y, Zhu Z, Zhang F, Kemper KE, Zheng Z, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat Commun. 2018;9(1):2941.
38. Titmuss A, Davis EA, Brown A, Maple-Brown LJ. Emerging diabetes and metabolic conditions among Aboriginal and Torres Strait Islander young people. MJA. 2019;210(3):111–3 e1.
39. Rogers AR, Bohlender RJ, Huff CD. Early history of Neanderthals and Denisovans. Proc Natl Acad Sci U S A. 2017;114(37):9859–63.
40. Pennisi E. Human evolution. More genomes from Denisova Cave show mixing of early human groups. Science. 2013;340(6134):799.
41. Juric I, Aeschbacher S, Coop G. The Strength of Selection against Neanderthal Introgression. PLoS Genet. 2016;12(11):e1006340.
42. Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, Kircher M, et al. A draft sequence of the Neandertal genome. Science. 2010;328(5979):710–22.
43. Prufer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, et al. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature. 2014;505(7481):43–9.
44. Martin SH, Jiggins CD. Interpreting the genomic landscape of introgression. Curr Opin Genet Dev. 2017;47:69–74.
45. Barton N, Bengtsson BO. The barrier to genetic exchange between hybridising populations. Heredity (Edinb). 1986;57 (Pt 3:357–76.
46. Malaspinas AS, Westaway MC, Muller C, Sousa VC, Lao O, Alves I, et al. A genomic history of Aboriginal Australia. Nature. 2016;538(7624):207–14.
47. Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, et al. A high-coverage genome sequence from an archaic Denisovan individual. Science. 2012;338(6104):222–6.
48. Taskent RO, Alioglu ND, Fer E, Melike Donertas H, Somel M, Gokcumen O. Variation and Functional Impact of Neanderthal Ancestry in Western Asia. Genome Biol Evol. 2017;9(12):3516–24.
49. Band G, Le QS, Jostins L, Pirinen M, Kivinen K, Jallow M, et al. Imputation-based meta-analysis of severe malaria in three African populations. PLoS Genet. 2013;9(5):e1003509.
50. Dolgova O, Lao O. Evolutionary and Medical Consequences of Archaic Introgression into Modern Human Genomes. Genes (Basel). 2018;9(7).
51. Gianfrancesco F, Esposito T, Casu G, Maninchedda G, Roberto R, Pirastu M. Emergence of Talanin protein associated with human uric acid nephrolithiasis in the Hominidae lineage. Gene. 2004;339:131–8.
52. Khrameeva EE, Bozek K, He L, Yan Z, Jiang X, Wei Y, et al. Neanderthal ancestry drives evolution of lipid catabolism in contemporary Europeans. Nat Commun. 2014;5:3584.
53. Dannemann M, Andres AM, Kelso J. Introgression of Neandertal- and Denisovan-like Haplotypes Contributes to Adaptive Variation in Human Toll-like Receptors. Am J Hum Genet. 2016;98(1):22–33.
54. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006;124(4):783–801.

55. Westwell-Roper C, Nackiewicz D, Dan M, Ehses JA. Toll-like receptors and NLRP3 as central regulators of pancreatic islet inflammation in type 2 diabetes. Immunol Cell Biol. 2014;92(4):314–23.
56. Sepehri Z, Kiani Z, Nasiri AA, Mashhadi MA, Javadian F, Haghighi A, et al. Human Toll like receptor 4 gene expression of PBMCs in diabetes mellitus type 2 patients. Cell Mol Biol (Noisy-le-grand). 2015;61(3):92–5.
57. Adegbija O, Hoy WE, Wang Z. Corresponding waist circumference and body mass index values based on 10-years absolute type 2 diabetes risk in an Australian Aboriginal community. BMJ Open Diabetes Res Care. 2015;3(1):e000127.
58. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med. 2008;359(21):2220–32.
59. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med. 2010;363(24):2339–50.
60. Vionnet N, Hani EH, Lesage S, Philippi A, Hager J, Varret M, et al. Genetics of NIDDM in France: studies with 19 candidate genes in affected sib pairs. Diabetes. 1997;46(6):1062–8.
61. Hemming R, Agatep R, Badiani K, Wyant K, Arthur G, Gietz RD, et al. Human growth factor receptor bound 14 binds the activated insulin receptor and alters the insulin-stimulated tyrosine phosphorylation levels of multiple proteins. Biochem Cell Biol. 2001;79(1):21–32.
62. Khan A, Hong-Lie C, Landau BR. Glucose-6-phosphatase activity in islets from ob/ob and lean mice and the effect of dexamethasone. Endocrinology. 1995;136(5):1934–8.
63. Goodarzi MO, Guo X, Taylor KD, Quinones MJ, Saad MF, Yang H, et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. Diabetes. 2004;53(1):214–20.
64. Ragolia L, Begum N. Protein phosphatase-1 and insulin action. Mol Cell Biochem. 1998;182(1–2):49–58.
65. Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008;40(6):768–75.
66. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009;41(1):25–34.
67. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet. 2008;40(6):716–8.
68. Diabetes Genetics Initiative of Broad Institute of H, Mit LU, Novartis Institutes of BioMedical R, Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007;316(5829):1331–6.
69. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science. 2007;316(5829):1341–5.
70. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science. 2007;316(5829):1336–41.
71. Daimon M, Sato H, Oizumi T, Toriyama S, Saito T, Karasawa S, et al. Association of the PIK3C2G gene polymorphisms with type 2 DM in a Japanese population. Biochem Biophys Res Commun. 2008;365(3):466–71.
72. Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, et al. Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels. Neuron. 1999;24(4):1037–47.
73. Kramps T, Peter O, Brunner E, Nellen D, Froesch B, Chatterjee S, et al. Wnt/wingless signaling requires BCL9/legless-mediated recruitment of pygopus to the nuclear beta-catenin-TCF complex. Cell. 2002;109(1):47–60.
74. Jin T. Current Understanding on Role of the Wnt Signaling Pathway Effector TCF7L2 in Glucose Homeostasis. Endocr Rev. 2016;37(3):254–77.
75. Ilich JZ, Kelly OJ, Kim Y, Spicer MT. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. Arhiv za higijenu rada i toksikologiju. 2014;65(2):139–48.
76. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. Am J Med. 1988;84(4):739–49.
77. Gracey M, Bridge E, Martin D, Jones T, Spargo RM, Shephard M, et al. An Aboriginal-driven program to prevent, control and manage nutrition-related "lifestyle" diseases including diabetes. Asia Pac J Clin Nutr. 2006;15(2):178–88.
78. Genne-Bacon EA. Thinking evolutionarily about obesity. Yale J Biol Med. 2014;87(2):99–112.
79. Frisch RE. Fatness, menarche, and female fertility. Perspect Biol Med. 1985;28(4):611–33.
80. Aschard H, Chen J, Cornelis MC, Chibnik LB, Karlson EW, Kraft P. Inclusion of gene-gene and gene-environment interactions unlikely to dramatically improve risk prediction for complex diseases. Am J Hum Genet. 2012;90(6):962–72.
81. Stenzel SL, Ahn J, Boonstra PS, Gruber SB, Mukherjee B. The impact of exposure-biased sampling designs on detection of gene-environment interactions in case-control studies with potential exposure misclassification. Eur J Epidemiol. 2015;30(5):413–23.
82. Baschetti R. Diabetes epidemic in newly westernized populations: is it due to thrifty genes or to genetically unknown foods? J R Soc Med. 1998;91(12):622–5.
83. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian aborigines after temporary reversion to traditional lifestyle. Diabetes. 1984;33(6):596–603.
84. Vaag AA, Grunnet LG, Arora GP, Brons C. The thrifty phenotype hypothesis revisited. Diabetologia. 2012;55(8):2085–8.
85. Fuchsberger C, Flannick J, Teslovich TM, Mahajan A, Agarwala V, Gaulton KJ, et al. The genetic architecture of type 2 diabetes. Nature. 2016;536(7614):41–7.
86. Field Y, Boyle EA, Telis N, Gao Z, Gaulton KJ, Golan D, et al. Detection of human adaptation during the past 2000 years. Science. 2016;354(6313):760–4.
87. Sebastio G, Villa M, Sartorio R, Guzzetta V, Poggi V, Auricchio S, et al. Control of lactase in human adult-type hypolactasia and in weaning rabbits and rats. Am J Hum Genet. 1989;45(4):489–97.
88. Ingram CJ, Mulcare CA, Itan Y, Thomas MG, Swallow DM. Lactose digestion and the evolutionary genetics of lactase persistence. Hum Genet. 2009;124(6):579–91.
89. Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. BMC Evol Biol. 2010;10:36.
90. Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, et al. Genetic signatures of strong recent positive selection at the lactase gene. Am J Hum Genet. 2004;74(6):1111–20.
91. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. Nat Genet. 2002;30(2):233–7.
92. Evershed RP, Payne S, Sherratt AG, Copley MS, Coolidge J, Urem-Kotsu D, et al. Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding. Nature. 2008;455(7212):528–31.

93. Tishkoff SA, Reed FA, Ranciaro A, Voight BF, Babbitt CC, Silverman JS, et al. Convergent adaptation of human lactase persistence in Africa and Europe. Nat Genet. 2007;39(1):31–40.
94. Perry GH, Dominy NJ, Claw KG, Lee AS, Fiegler H, Redon R, et al. Diet and the evolution of human amylase gene copy number variation. Nat Genet. 2007;39(10):1256–60.
95. Santos JL, Saus E, Smalley SV, Cataldo LR, Alberti G, Parada J, et al. Copy number polymorphism of the salivary amylase gene: implications in human nutrition research. J Nutrigenet Nutrigenomics. 2012;5(3):117–31.
96. Luca F, Bubba G, Basile M, Brdicka R, Michalodimitrakis E, Rickards O, et al. Multiple advantageous amino acid variants in the NAT2 gene in human populations. PLoS One. 2008;3(9): e3136.
97. Hancock AM, Witonsky DB, Ehler E, Alkorta-Aranburu G, Beall C, Gebremedhin A, et al. Colloquium paper: human adaptations to diet, subsistence, and ecoregion are due to subtle shifts in allele frequency. Proc Natl Acad Sci U S A. 2010;107(Suppl 2):8924–30.
98. Kernie SG, Liebl DJ, Parada LF. BDNF regulates eating behavior and locomotor activity in mice. EMBO J. 2000;19(6):1290–300.
99. Gray J, Yeo G, Hung C, Keogh J, Clayton P, Banerjee K, et al. Functional characterization of human NTRK2 mutations identified in patients with severe early-onset obesity. Int J Obes. 2007;31(2):359–64.
100. Yilmaz Z, Kaplan AS, Tiwari AK, Levitan RD, Piran S, Bergen AW, et al. The role of leptin, melanocortin, and neurotrophin system genes on body weight in anorexia nervosa and bulimia nervosa. J Psychiatr Res. 2014;55:77–86.
101. Peyregne S, Boyle MJ, Dannemann M, Prufer K. Detecting ancient positive selection in humans using extended lineage sorting. Genome Res. 2017;27(9):1563–72.
102. Ruhli FJ, Henneberg M. New perspectives on evolutionary medicine: the relevance of microevolution for human health and disease. BMC Med. 2013;11:115.
103. Grafen A. Biological fitness and the fundamental theorem of natural selection. Am Nat. 2015;186(1):1–14.
104. Piegorsch WW. Fisher's contributions to genetics and heredity, with special emphasis on the Gregor Mendel controversy. Biometrics. 1990;46(4):915–24.
105. Henneberg MPJ. Biological state index of human groups. Przeglad Antropologiczny. 1975;41:191–201.
106. (AIHW) AIoHaW. National (insulin-treated) Diabetes Register (2016)
107. Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. Nat Med. 2001;7(8):899–905.
108. Pociot F. Type 1 diabetes genome-wide association studies: not to be lost in translation. Clin Transl Immunology. 2017;6(12):e162.
109. Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997–2010: a national Australian registry-based cohort study. Diabetologia. 2016;59(6): 1177–85.
110. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008–2010. JAMA. 2015;313(1):37–44.
111. Wiebe JC, Santana A, Medina-Rodriguez N, Hernandez M, Novoa J, Mauricio D, et al. Fertility is reduced in women and in men with type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium (T1DGC). Diabetologia. 2014;57(12):2501–4.
112. Elhamamsy AR. DNA methylation dynamics in plants and mammals: overview of regulation and dysregulation. Cell Biochem Funct. 2016;34(5):289–98.
113. Ling C, Ronn T. Epigenetics in Human Obesity and Type 2 Diabetes. Cell Metab. 2019;29(5):1028–44.
114. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000;49(12):2208–11.
115. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev. 2006;82(8):485–91.
116. Chen P, Piaggi P, Traurig M, Bogardus C, Knowler WC, Baier LJ, et al. Differential methylation of genes in individuals exposed to maternal diabetes in utero. Diabetologia. 2017;60(4):645–55.