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THE EVOLUTION OF TYPE II DIABETES MELLITUS: HOW THE MALADAPTIVE DISEASE CONTINUES TO SURVIVE SELECTIVE PRESSURES.

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Abstract

Over twenty-five years of research into diabetes type two mellitus, a working hypothesis has formed to advance the development of precision therapy for this condition. Previous studies that used amplified genomic DNAs for genome-wide searches of human genes misled many researchers. However, a recent investigation used next-generation RNA sequencing to demonstrate a crucial down-regulation of two genes, TPD52L3 and NKX2-1. This compendium covers key principles for understanding the hypothesis, including glucose effectiveness, genetics, atomistic glucose and glucose transport, β-cell functions, insulin sensitivity, free fatty acids, cell membranes, membrane flexibility, and pre-diabetes type 2. Furthermore,this paper will evaluate the T2D enigma from a genetic and evolutionary standpoint with the aim of gaining insight into the reasons that underpin the growing genetic predisposition and positive natural selection of T2D.This paper will evaluate the T2D enigma from a genetic and evolutionary standpoint with the aim of gaining insight into the reasons that underpin the growing genetic predisposition and positive natural selection of T2D.This paper additionallyaddresses the 10 evolutionary questions associated with disease vulnerability.

Key Words: Type two diabetes, insulin resistance, monogenic inheritance, polygenic subset, health outcomes.

1.0. Introduction

Diabetes Mellitus (DM) is a disease not transmitted by a pathogen capable of switching isotypes and evading human bodily detection, but instead, it is caused by much more insidious and surreptitious invader: the western way of life. DM is multifactorial, showing clinically due to a number of interrelated factors including genetics, diet and lifestyle (Kahn, Cooper, & Del Prato, 2014). The disease is classified into three subtypes: type I (non-insulin dependent diabetes mellitus, NIDDM), type II (insulin dependent diabetes mellitus, IDDM), and Diabetes Insipidous. The variation between these pathologies relates largely to aetiology. Type I DM (T1D) is an inborn condition characterised by autoimmune destruction of pancreatic islet cells that produce insulin, a hormone that promotes the uptake of glucose into cells. On the other hand, type II DM (T2D) is an acquired condition, whereby pancreatic β-cells become desensitized to insulin (insulin resistance), resulting in an inability to absorb free glucose. Diabetes insipidous is a rare condition with hallmark hypersecretion of vasopressin that regulates kidney function.

The uneven geographical distribution of DM is both curious and evolutionarily puzzling. The question remains as to why the gene variants continue to persist in the gene pool and underpin the disease when associated gene variants should be limited by natural selection (Ayub et al., 2014; Ségurel et al., 2013). This paper will evaluate the T2D enigma from a genetic and evolutionary standpoint with the aim of gaining insight into the reasons that underpin the growing genetic predisposition and positive natural selection of T2D. In particular, this paper will address the 10 evolutionary questions associated with disease vulnerability put forward by Nesse (2011). Further understanding of the genetic evolution of T2D will advance medical applications to alleviate the significant health, economic and mortality burden of the disease (Bonnefond, Froguel, & Vaxillaire, 2010).

2.0. Pathophysiology of Type II Diabetes Mellitus

Glucose homeostasis is managed through a series of feedback mechanisms featuring the pancreatic β-cells, which secrete insulin, and various insulin-sensitive tissues that are therefore highly dependent on β-cell responses to increasing glucose concentrations (Kahn et al., 2014). Proportionally high levels of insulin secretion are capable of overcoming rising insulin-resistance by β-cells in order to facilitate homeostatic glucose control (Kahn et al., 2014). In T2D, β-cells become incapable of delivering adequate insulin to sensitize tissues to glucose, leading to consequential rises in serum glucose levels (Kahn et al., 2014). The insufficiency of β-cells is both genetic and environmental in nature, with several distinct body systems playing a role (Bonnefond et al., 2010; Kahn et al., 2014). It is presently recognised that both inadequate insulin secretion and insulin resistance are linked to T2D (Florez, 2008; Kahn et al., 2014).

The complication of T2D can be potentially fatal if unmanaged. Uncontrolled glucose can lead to hypoglycemic attacks, hyperosmolar hyperglycemic nonketotic syndrome (HHNS), and various vasculopathies, including microvascular complications within the eye, kidney and nerves, and macrovascular complications within the heart, brain and peripheral blood supply (Kahn et al., 2014). Collectively these consequences may further rapid renal and cardiac failure, as well as risks of cerebrovascular accidents (i.e. stroke), and significantly diminish ones quality of life.

Of central importance to this paper is the difference between early-onset and adult-onset T2D variants. The first, early-onset subtype, is recognised to occur through monogenic inheritance, while the second is linked to polygenic traits and is commonly acquired rather than inherited (Gregg, Gu, Cheng, Narayan, & Cowie, 2007; Stumvoll, Goldstein, & van Haeften, 2005). Both genetically and pathologically, this variation may provide an explanation to the survivorship of T2D alleles within the gene pool.

3.0. Genetics of Type II Diabetes Mellitus (T2D)

Medical and evolutionary genetics continues to play an important role in our understanding of disease (Nesse, 2011). Of particular significance in this case of T2D is the evolutionary development of humans, not simply for positive adaptations, but for seemingly maladaptive traits that continue to permit and progress disease (Nesse, 2005) (Crespi, 2000). Indeed, no valid method for formulating hypotheses and testing maladaptive traits and their development exists, making it difficult to understand the causational genetics that render humans vulnerable to diseases such as T2D.

Genetic contributions to T2D are widely recognised for both early-onset T2D, which is identified as being primarily monogenic (Table 1), and adult-onset (Table 2) subtypes (Gregg et al., 2007; Kahn et al., 2014; Stumvoll et al., 2005). Through inquiry into the distinct T2D variants, it is evident that significant genetic heterogeneity is present among subtypes, illustrating the convoluted nature of β-cell signaling pathways (Florez, 2008). As previously mentioned, T2D pathogenesis has been shown to include both insulin resistance and β-cell dysfunction resulting in a decrease in insulin secretion (Florez, 2008).

Evidence that is fundamental in demonstrating the genetic and evolutionary characteristics of T2D is the link between relatives. T2D has a high concordance rate (approximately 70%) between monozygotic twins compared to the lower concordance in dizygotic twins, which is 20-30% (Kaprio et al., 1992). The intergenerational genetic relationship is also an important metric. Children whose parents have T2D have a 40% lifetime risk of developing the condition. Moreover, this figure is greater if the mother is diabetic and significantly greater—up to 70% lifetime risk—if both parents suffer T2D (Groop et al., 1996). Prospectively, studies have demonstrated a double increase in the likelihood of T2D in those with first-degree family history (Lyssenko et al., 2008) (Lyssenko et al., 2005). An explanation as to why T2D relatives have such a high risk of developing the condition remains challenging.

Genome-wide association studies (GWAS) have demonstrated greater than 50 gene loci related to T2D (Morris et al., 2012). Furthermore, 53 gene loci have connected to serum insulin and glucose concentrations and a significant proportion of these (33 gene loci) have been linked to T2D (Morris et al., 2012; Sniderman, Bhopal, Prabhakaran, Sarrafzadegan, & Tchernof, 2007). Interestingly, while some of the genetic material demonstrated to be associated with T2D, a small proportion code for known products (Kahn et al., 2014). Finally, the T2D gene associations provide little benefit in prediction of disease risks compared to conventional clinical indicators (Lyssenko et al., 2008).

Table 1. Monogenic subtypes of T2D. Adapted from Bonnefond et al. (2010). The emerging genetics of type 2 diabetes. *Trends in molecular medicine*, *16*(9), 407-416.

Gene name (locus)	Protein	Protein function	Diabetes phenotype
MODY			
HNF4A (20q12)	HNF4α	Transcription factor	MODY1, in adolescence or early adulthood (and neonatal hyperinsulinism)
GCK (7p15)	Glucokinase	Glucose phosphorylation	MODY2, mild hyperglycemia (onset in early childhood, and lifelong) [frequent]
HNF1A (12q24)	HNF1α	Transcription factor	MODY3, in adolescence or early adulthood [frequent]
PDX1 (13q12)	IPF1	Transcription factor	MODY4, in early adulthood (similar to *HNF1A* but rare)
HNF1B (17q21)	HNF1β	Transcription factor	MODY5, in early adulthood, renal cysts and diabetes (RCAD)
NEUROD1 (2q32)	Beta2	Transcription factor	MODY6, in early adulthood (similar to *HNF1A* but rare)
INS (11p15.5)	Preproinsulin, insulin	Hormone, hypoglycemic effect and on anabolism	MODY7, in childhood and early adulthood
ND			
PLAGL1 (6q24)	Pleiomorphic adenoma gene-like 1	Nuclear zinc finger protein	Transient ND; Chromosome 6q structural anomalies with imprinting mechanisms (methylation defects)
KCNJ11 (11p15.1)	Kir6.2	K channel pore-forming subunit	Permanent and transient ND
ABCC8 (11p15.1)	SUR1	K channel regulatory subunit and sulfonylurea receptor	Permanent and transient ND
GCK (7p15)	Glucokinase	Glucose phosphorylation	Permanent ND for homozygous mutations
INS (11p15.5)	Insulin	Hormone, hypoglycemic effect and on anabolism	Permanent ND and early-infancy diabetes; Heterozygous mutations in *INS* coding regions/homozygous mutations in *INS* regulatory regions
ND associated with developmental anomalies and/or extra-pancreatic features			
PDX1 (13q12)	IPF1	Transcription factor	Pancreas agenesis and ND for homozygous mutations
EIF2AK3 (2p12)	PERK	Pancreatic eIF2-alpha kinase	Wolcott-Rallison syndrome (diabetes associated with epiphyseal dysplasia)
PTF1A (10p12)	Pancreas-specific transcription factor 1a	Transcription factor	ND associated with pancreatic hypoplasia and cerebellar hypoplasia
GLIS3 (9p24.2)	GLI-similar 3 transcription factor	Transcription factor	ND associated with congenital hypothyroidism (NDH syndrome)
FOXP3 (Xp11.23)	Forkhead box P3	Transcription factor	X-linked IPEX syndrome (with diffuse autoimmunity)
HNF1B (17q21)	HNF1β	Transcription factor	Transient ND associated with pancreatic atrophy and/or renal anomalies

Table 2. T2D susceptibility genes and genetic loci. Adapted from Bonnefond et al. (2010). The emerging genetics of type 2 diabetes. *Trends in molecular medicine*, *16*(9), 407-416.

Gene (suggested)	Locus	Protein	Assumed effect of risk allele
Biological candidate gene studies			
PPARG	3p25	Peroxisome proliferator-activated receptor-γ	Decreased insulin sensitivity, decreased insulin clearance
KCNJ11	11p15.1	K inwardly-rectifying channel, subfamily J, member 11	Decreased β-cell function, decreased glucose-stimulated insulin secretion (GSIS), decreased insulin sensitivity
HNF1B	17cen-q21.3	Hepatocyte nuclear factor 1-beta	Decreased β-cell function
WFS1	4p16	Wolfram syndrome 1 (wolframin)	Decreased β-cell function, decreased insulin secretion
GCK	7p15.3-p15.1	Glucokinase (Hexokinase 4)	Decreased β-cell function, decreased GSIS, increased fasting glucose, increased glycated hemoglobin
Exploration of linkage peaks			
TCF7L2	10q25.3	Transcription factor 7-like 2 (T-cell-specific, HMG-box)	Decreased β-cell function, decreased incretin-stimulated insulin secretion, decreased GSIS, decreased proinsulin conversion, decreased insulin sensitivity, decreased disposition index, increased fasting glucose, increased 2h-glucose
GWAS for T2D			
CDKN2A/2B	9p21	Cyclin-dependent kinase inhibitor 2A/2B	Decreased β-cell function, decreased GSIS, decreased disposition index
CDKAL1	6p22.3	CDK5 regulatory subunit associated protein 1-like 1	Decreased β-cell function, decreased GSIS, decreased proinsulin conversion, decreased disposition index
SLC30A8	8q24.11	Solute carrier family 30 (zinc transporter), member 8	Decreased β-cell function, decreased GSIS, decreased proinsulin conversion, decreased disposition index, increased fasting glucose, increased 2h-glucose, increased glycated hemoglobin
IGF2BP2	3q27.2	Insulin-like growth factor 2 mRNA binding protein 2	Decreased β-cell function, decreased GSIS, decreased disposition index
THADA	2p21	Thyroid adenoma associated	Decreased β-cell function, decreased insulin sensitivity, decreased second-phase insulin secretion, decreased disposition index, decreased GLP-1 and arginine-stimulated insulin response
NOTCH2	1p13-p11	Neurogenic locus notch homolog protein 2 (*Drosophila*)	NA
CDC123	10p13	Cell division cycle 123 homolog (*Saccharomyces cerevisiae*)	Decreased β-cell function, decreased insulin secretion
CAMK1D		Calcium/calmodulin-dependent protein kinase type 1D	
HHEX	10q23	Hematopoietically expressed homeobox	Decreased β-cell function, decreased GSIS, decreased insulin sensitivity, decreased proinsulin conversion, decreased disposition index
IDE		Insulin-degrading enzyme	
TSPAN8	12q14.1-q21.1	Tetraspanin 8	Decreased β-cell function, decreased insulin secretion, decreased insulin sensitivity
LGR5	12q22-q23	Leucine-rich repeat-containing G protein-coupled receptor 5	
ADAMTS9	3p14.3-p14.2	ADAM metallopeptidase with thrombospondin type 1 motif, 9	Decreased insulin sensitivity
JAZF1	7p15.2-p15.1	Juxtaposed with another zinc finger protein 1	Decreased β-cell function, increased insulin secretion, increased fasting insulin
IRS1	2q36	Insulin receptor substrate 1	Increased insulin resistance, decreased insulin sensitivity, increased fasting insulin, increased 2h-insulin
KCNQ1	11p15.5	K voltage-gated channel, KQT-like subfamily, member 1	Decreased β-cell function, decreased insulin secretion, decreased incretin secretion
FTO	16q12.2	Fat mass and obesity-associated protein	Increased risk of obesity, increased body mass index, increased fat mass, increased triglycerides and cholesterol
GWAS for T2D-related traits			
GCKR	2p23	Glucokinase (hexokinase 4) regulator	Increased insulin resistance, increased fasting insulin, increased fasting glucose, increased 2h-glucose
MTNR1B	11q21-q22	Melatonin receptor 1B	Decreased β-cell function, decreased GSIS, decreased disposition index, increased fasting glucose, increased glycated hemoglobin
ADCY5	3q13.2-q21	Adenylate cyclase 5	Decreased β-cell function, increased fasting glucose, increased 2h-glucose
PROX1	1q32.2-q32.3	Prospero homeobox 1	Decreased β-cell function, increased fasting glucose
DGKB	7p21.2	Diacylglycerol kinase, beta 90 kDa	Decreased β-cell function, increased fasting glucose
TMEM195		Transmembrane protein 195	

4.0. Evolutionary Theories for the Positive Selection of Type II Diabetes

The plethora of underlying genetic mechanisms of T2D, both monogenic and polygenic, renders difficulty in establishing an evolutionary rationale for its survivorship as a disease trait. Multiple trait analysis is required to assess the evolution of T2D within the polygenic subset, and therefore variation in traits among groups appears to limit genetic and evolutionary discourse. Nonetheless, the polygenic variant represents the opportunity for exploring the uniform traits.

Up to 65 predisposing genetic loci have been identified in both genome-wide and candidate gene studies, with the association signal being determined by alleles on common haplotypes (Ayub et al., 2014). Moreover, fine-mapping and transethnic data suggest with a significant degree of scientific vigour, a single causal allele (Maller et al., 2012). Nonetheless the discovery of a single causative allele remains elusive.

One explanation for why T2D genes remain in the gene pool is the so-called 'thrifty genotype hypothesis' described first by Neel (1962). This concept links genotypic evolution to the metabolic thrift (*i.e. susceptibility*) of human ancestry exposed to successive cycles of feast and famine (Wells, 2009). Accordingly, therefore, humans would demonstrate this thrifty adaptation in response to both abundant food and hallmark contemporary sedentism of western life, subsequently predisposing to diseases such as T2D and obesity (Ayub et al., 2014; Neel, 1962; Wells, 2009). More specifically, the thrift hypothesis would then suggest that the rapid insulin response to intermittent feeding was an asset to hunter-gatherers, primarily because it minimisedglucosuria as result of renal glucose secretion (Neel, Weder, & Julius, 1998). Indeed, this response seems to align with the environmental demands of the day and may subsequently explain the susceptibility of humans now that hyperalimentation is common throughout the developed world.

There is alternate hypothesis to that proposed by Neel (1962) that suggests the presence of protective (non-thrifty) rather than susceptibility (thrifty) alleles. Indeed, it is possible like many genetic traits that the T2D phenotype is expressed according to the unique interplay between many protective and susceptibility genes. Firstly, several studies have been unsuccessful in detecting risk alleles (Chen et al., 2012; Klimentidis, Abrams, Wang, Fernandez, & Allison, 2011; Ségurel et al., 2013). However, these studies have been based on small loci datasets. Nevertheless all of these studies favoured the possibility that positively selected protective alleles are more likely at play. Indeed, as demonstrated by Ségurel et al. (2013) it is possible that selection shows a shift from metabolic thrift to protective alleles that have become advantageous according to population dynamics such as lifestyle and dietary intake. It is genetically plausible that selective pressures have reshuffled according to the dietary changes associated with Western nations, and hence this may be the reason for ongoing T2D susceptibility and/or productivity within these populations.

Table 3. *Addressing the ten evolutionary questions of disease vulnerability*

Addressing the ten evolutionary questions of disease vulnerability
Nesse (2011) proposes ten questions of evolutionary studies of disease vulnerability under four major tasks: 1) precisely defining the object of explanation; 2) specifying the kind of explanation sought; 3) listing and considering all viable hypothesis; and 4) describing the methods used for hypothesis testing. This paradigm is both useful for and relevant to analysing the high degree of susceptibility associated with T2D. The remaining part of this paper will be committed to answering the questions defined under each of Nesse's (2011) tasks.
Task 1 – precisely defining the object of explanation
T2D takes on two genetic forms, monogenic and polygenic that represent complexity in considering the reasons for disease progression, and therefore relies on a broad scope when assessing the condition. Evidently the polygenic form is both less understood and more prevalent, and for this reason is more applicable to future improvements in health initiatives. Indeed, as this is the case, cross-sectional analyses such as that performed by Ségurel et al. (2013) are crucial to our evolutionary understanding of the shifts in genetic pressures associated with the geographic and lifestyle factors linked to varying groups.
Task 2 – specifying the kind of explanation sought
The objective must be focused on obtaining a superior understanding of the significant genotypic links among groups with T2D. The subsequently goal must subsequently be to explain the phylogenic progression and selective pressures that shape the disease progression. A number of larger and smaller studies have found substantial connections between the genetics and evolutionary survivorship of T2D. Genetic and evolutionary discourse around the condition highlights a polymorphic pattern with ample evidence to suggest that T2D is underpinned by maladaptive genetic variations. The question remains as to the evolutionary advantages of the protective and/or susceptibility genes that continue to promote phenotypic expression of T2D.
Task 3 – listing and considering the viable hypotheses
There are two major hypotheses formulated to explain the evolution of T2D: the thrifty or susceptibility hypothesis and the non-thrifty or protective gene hypothesis. As the first possible hypothesis generated to explain the progression of T2D, the thrifty hypothesis has seen impetus in the body of literature. More contemporary findings propose that protective alleles rather than susceptibility alleles are to blame for T2D persistence. It appears that the dual consideration of a net outcome has been under-considered within the literature. Given the polygenic nature of T2D in adults, it appears possible that the genetic basis of the disease

is both, succumbing to the susceptibility factors in those that express the disease and holding a greater genetic protective capacity in those that do not. Subsequently, this brings forth the presence of selective pressures and their role in the evolution of T2D. As a result of variation between populations, it is proposed that both diet and lifestyle play a role in the body's genetic selection and its physiologic or pathologic reactions.

Task 4 – describing the methods used to test the hypothesis

Multiple methods have been employed in the research of T2D genetics and evolution. A significant proportion has been directed towards identifying the various protective or risk alleles associate with the condition utilising genomic analysis and GWAS. Some effort has been assigned to comparative analysis of groups and considerations of the abovementioned genetic variables. Nonetheless, research more cross-sectional research needs to be perfomed, taking particular note of the influences on genetic factors that may be present in specific populations or at specific locations.

There are multiple explanations for the why the genetic puzzle of T2D remains so. Firstly, while research has touched on the 'characteristics' of the various T2D traits, no established theory explains why T2D is considered positive trait within an evolutionary paradigm. The evolutionary merit of the trait is largely limited to the thrift hypothesis, which explains its benefit in times of cycling famine and feasting.

5.0. Conclusion

The evolutionary underpinnings of T2D remain an enigma. This essay has explored the genetics and evolutionary perspectives that are frontrunners in elucidating the evolutionary advantage of, and reasons for, T2D positive selection. Whether T2D allele selection occurs in alignment with thrifty (i.e. susceptibility) or non-thrifty (i.e. protective) theories is polarizing. Indeed, the net combined outcome is one possible synthesis of the findings. Unfortunately, when comparing the current clinical utility of genetic screening to the non-genetic screening factors of T2D, the data fails to provide convincing evidence to support the former. Further cross-sectional analysis and genome studies need to focus on explaining the mechanisms behind the phylogenic strength of T2D, in order to facilitate an enhanced understanding and improved capacity to harness such knowledge in augmenting health outcomes and reducing the burden of T2D.

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