



Genotrim™, a DNA-customized nutrigenomic product, targets genetic factors of obesity: Hypothesizing a dopamine–glucose correlation demonstrating reward deficiency syndrome (RDS)

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Received 10 July 2006; accepted 22 August 2006

Summary Obesity is the second largest cause of preventable death in the United States. Historically, obesity was considered a behavioral problem that could be simply addressed with behavioral modifications in diet and exercise. As scientific advancements have demonstrated in other neurological healthcare conditions such as alcoholism, there are important biological and genetic components that limit the efficacy of behavioral adjustments alone. In light of data suggesting frequent co-morbidities to obesity, including diabetes mellitus, atherosclerosis, osteoporosis, and potentially others, we hypothesize that the biologic and genetic factors, synergistically with behavioral modifications, must be addressed to adequately treat this disease. We hypothesize that one such genetic factor that influences behavior and thus obesity is a predisposition to glucose craving and the overall effect of dopaminergic activity in the reward center of the brain. This defect drives individuals to engage in activities of behavioral excess, which will

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increase brain dopamine function, for which we have created the term reward deficiency syndrome (RDS) to categorize such biological influences on behavior. Consuming large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates the brain's production of and utilization of dopamine. So too does the intake of crack/cocaine and the abuse of nicotine. We are proposing that a novel approach to nutritional supplementation may be required to target the RDS role in obesity. In this regard, Genotrim™, a DNA based customized nutraceutical has been designed and is currently under investigation in several clinical studies. This is the first hypothesis paper whereby this new paradigm shift in thinking about obesity is presented.

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Introduction

Obesity used to be understood in fairly elementary behavioral terms: excess body weight resulting from eating too much and exercising too little, due in large part to a lack of willpower or self-restraint. But as people have increased their dieting and exercise, the rates of obesity continue to rise as the combined prevalence of overweight and obesity in the US has increased from 46% of the adult populations (NHANES II, 1976–1980) to over 60% of the adult population in NHANES III (1988–1994). In 1985, obesity was recognized as a chronic medical disease with serious health implications caused by a complex set of factors. Obesity-related medical conditions contribute to 300,000 deaths each year, second only to smoking as a cause of preventable death [1]. Obesity has been established as a major risk factor for hypertension, cardiovascular disease, Type 2 diabetes, and some cancers in both men and women. Obesity affects 58 million people across the nation and its prevalence is increasing (source: US Census Bureau). Approximately one-third of American adults are estimated to be obese, and 60% are overweight.

In response to this rising epidemic, the medical, food and fitness communities have consistently told Americans to just make behavioral modifications, such as diet and exercise. As scientific advancements have demonstrated in other neurological healthcare conditions such as alcoholism, there are important biological and genetic components that limit the efficacy behavioral adjustments alone. In a recent study of 11,000 Americans, results suggested that more than 75% of obese Americans ($n=3,100$) say they have healthy eating habits. According to this survey, 40% of obese people also said they do "vigorous" exercise at least three times per week. In this survey by Thomson Medstat, a Michigan-based healthcare research firm, obese people reported similar behaviors in snacking, reading nutritional labels, and eating out when compared to normal weight people [2].

Weight loss, alone, is difficult, but sustainable weight loss is also exceedingly difficult. Most people regain as much as two-thirds of weight lost within one year and regain all of it or more than was initially lost, within five years.

Sixteen years ago, Blum et al. published landmark research suggesting that another prevalent healthcare condition which had been traditionally characterized in behavioral terms like obesity, namely alcoholism, also had a hereditary or genetic component and that genetic information could explain why such a condition could be found to "run in the family". Blum's research [3] continued to explain how knowing this important genetic information could then caution certain genotypes to adjust their dietary intake and environments to overcome this genetic predisposition. Like alcoholism, obesity may be due in part to certain genetic predispositions; and by the body engaging in behavior to overcome these deficiencies, the host may engage in behaviors that are individually unhealthy or detrimental.

This initial research began to explain a concept which has now been defined as reward deficiency syndrome and we hypothesize that understanding dopaminergic genetic predisposition and then using that information to modulate dopamine will be a route to treat obesity. We hypothesize and will explain a link between dopaminergic activity and glucose metabolism. And we propose that a genetically-guided or customized nutritional regimen, such as GenoTrim, is optimal to achieve the intended impact on dopamine and glucose metabolism.

Reward deficiency syndrome

The reward deficiency syndrome (RDS) [4,5] results from a dysfunction in the Brain Reward Cascade, which directly links abnormal craving behavior with a defect in the DRD₂ dopamine receptor gene as well as other dopaminergic genes (D1, D3, D4, D5). Dopamine is a very powerful neurotransmitter in the brain that controls feelings of well being.

This sense of well being is produced through the interaction of dopamine and neurotransmitters such as serotonin, the opioids, and other powerful brain chemicals. Low serotonin levels are associated with depression. High levels of the opioids (the brain's opium) are associated with a sense of well being. The complex interactions of these powerful neurotransmitters ultimately regulating the dopaminergic activity in the Reward Center of the Brain, which has been termed by Blum and Koslowski, "The Brain Reward Cascade" [6]. This cascade and the genes involved provides a targeted blueprint for potential obesity treatment.

Reward Deficiency Syndrome involves a form of sensory deprivation of the brain's reward or pleasure mechanisms. The reward deficiency syndrome can be manifested in relatively mild or severe forms that follow as a consequence of an individual's biochemical inability to derive reward from ordinary, everyday activities. We believe that we have discovered at least one genetic variation that leads to an alteration in the reward pathways of the brain. It is a variant form of the gene for the dopamine D₂ receptor, called the A1 allele. This genetic variant also is associated with a spectrum of impulsive, compulsive, and addictive behaviors. The concept of the Reward Deficiency Syndrome unites those disorders and may explain how simple genetic anomalies give rise to complex aberrant behavior [7,8].

Role of the DRD2 gene in RDS and obesity

In individuals possessing an abnormality in the DRD2 Dopamine Receptor Gene, the brain lacks enough dopamine receptor sites to use the normal amount of dopamine in the Reward Center of the brain and thus reduces the function of dopamine in this area of the brain [8,9]. Humans possessing the A1 variant in the Dopamine D2 Receptor Gene tend to be serious illicit drug abusers, may have unhealthy appetites which lead to obesity or overeating or on the other extreme be anorexic with extremely low caloric intake, have levels of stress [10] over an extended time period and their addictive brains lead to high generalized craving behavior. In essence they seek substances including alcohol, cocaine, nicotine, and or glucose (substances known to cause preferential release of dopamine at the *nucleus accumbens*, the reward site of the brain) to activate dopaminergic pathways as a self-healing process to offset their low D2 receptors caused by genetic antecedents known as the dopamine D2 receptor gene Taq1 A1 allele [8,11,12].

One important study from Nora Volkow's group further provides support for the role of the dopamine D2 receptor gene in alcohol intake in rats. Utilizing a cDNA construct of the dopamine D2 receptor gene implanted into the *n. accumbens* of rats, they found that following a four-day treatment, the dopamine D2 receptors increased to 150% above pretreatment level and alcohol drinking was reduced by 50%. After a period of eight days, the D2 receptor density returned to pretreatment level as did alcohol drinking. Twenty-four days later, second injections of the same construct caused a similar increase in density with a two-fold decrease in drinking [13]. Additionally the same group reported low D2 receptors in ten obese subjects using Pet scanning techniques compared to non obese controls. The D2 receptor paucity also correlated with high body mass index (BMI) [14].

In another study, Spits and associates (1997) [15] found that dopamine D2 receptor gene variant A1 allele was significantly associated in obese individuals than in lean controls. Most recently this work has been supported by Fang et al. [16]. This group has previously reported that the Taq 1 polymorphism of the dopamine D2 receptor (DD2R) gene is associated with both blood pressure and obesity indices in a normoglycaemic Hong Kong Chinese population. In their most recent study Fang and associates present evidence confirming the linkage between this gene polymorphism, obesity and hypertension. Thus the authors concluded that dopamine modulates a variety of physiological functions including natriuresis and satiety.

With regard to the concept that within the reward deficiency syndrome (RDS) hypothesis [3,17] genetic commonality exist between a number of dopaminergic activating substances such as alcohol and opiates and possibly even glucose, evidence now exists that intermittent, excessive sugar intake causes endogenous opioid dependence. In rats, repeated, excessive intake of sugar created a state in which an opioid antagonist caused behavioral and neurochemical signs of opioid withdrawal. The indices of anxiety and DA/ACh imbalance were qualitatively similar to withdrawal from morphine or nicotine, suggesting that rats have become sugar-dependent [18]. In terms of understanding the brain reward cascade, there is evidence that serotonergic activation may also influence dopamine D2 receptor function. This is important when we consider the so called "sweet tooth". Therefore the work by Kogan et al. [19] confirms that the drug DR4004, a putative 5-HT₇ receptor antagonist, also has functional activity at the dopamine D2 receptor. It is of interest that neuroanatomical data sug-

gest a potentially interactive role between accumbens (NAcc), acetylcholine (ACh) and dopamine. There is evidence that NAcc ACh is apparently related to neural processes underlying not only psychostimulant reward but also natural consummatory behavior i.e. feeding. In this regard, Hajnal et al. [20] found that accumbens cholinergic interneurons play a role in the regulation of body weight and metabolism. In this context both stress and the role of dopamine play an important part in the ACh response.

Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese subjects may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. The authors conclude that strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals.

Dopamine–glucose link

To understand the important relationship between dopamine and glucose, it is of utmost importance to realize that in the meso-limbic system the glucose receptor is in close proximity with the enkephalinergic neurons. There are also other important connections in the substantia nigra, tuberoinfundibular neurons, globus pallidus, and other important brain regions.

It is well known that glucose modulates substantia nigra (SN) dopamine neuronal activity and GABA terminal transmitter release by actions of an ATP-sensitive potassium channel. In a study by Levin et al. [21], the effect of altering SN glucose levels on striatal dopamine release was assessed by placing microdialysis probes into both the SN and striatum of male rats. During 50 mM glucose infusion, striatal DA efflux increased transiently by 50% and returned to baseline after 60 min. Moreover, efflux increased by a further 30% when GABA (A) antagonist bicuculline was added. Furthermore, at basal glucose levels, nigral bicuculline alone raised striatal dopamine efflux by 31% suggesting the well-known tonic GABA inhibitory input to the DA neurons. Thus striatal dopamine release is affected by changing SN glucose levels. According to Levin and associates, this response may reflect the known effect of glucose on K(ATP) channel activity on both SN Dopamine neurons and GABA axon terminals in the SN. These interactions could provide a mechanism whereby glucose modulates motor activity involved in food intake.

Koshimura et al. [22] found that long-term incubation with high concentration of glucose in-

creased the capacity of Calcium uptake to enhance depolarization-induced dopamine release from Pheochromocytoma–12 cells. These data taken together suggest that a high concentration of glucose induced activation of the calcium channel stimulates dopamine release from P12 cells.

Bello et al. [23] found that restricted feeding with scheduled sucrose access results in an up-regulation of the rat dopamine transporter in the *n. accumbens* and ventral tegmental area of the brain. Moreover, it is known that dopamine can activate B₃ adrenoreceptors to lower glucose uptake into rat white adipocytes which lack dopaminergic receptors. It is of interest that intrastriatal injection of D₁ and D₂ dopamine agonists affects glucose utilization in both the direct and indirect pathways of the rat basal ganglia [24]. Moreover, dopamine receptor antagonism can influence fat intake in rats dependent upon dosage and time after treatment. In this regard, both D₁ and D₂ receptor co-activation significantly reduced body weight, body fat, food consumption and serum concentrations of glucose, triglycerides, free fatty acid and insulin while increasing protein mass [19]. Furthermore, studies on blood glucose found blood glucose concentrations to be significantly correlated with cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid [25].

It is well known that pharmacologic doses of the glucose analogue, 2-deoxyglucose (2DG) cause acute glucoprivation and are associated with enhanced dopamine turnover in preclinical studies. In fact, lines of evidence indicate that a variety of metabolic stressors, including acute glucose deprivation are associated with dopamine release. Using PET, Adler et al. [26] found that 2DG administration enhanced synaptic dopamine concentrations. The administration of 2DG is associated with significant striatal dopamine release even in healthy volunteers. These data are important because it further closely ties glucose levels to dopaminergic activity. Moreover, there is even a relationship between insulin levels and dopamine release in the tuberoinfundibular neurons. The insulin effect is dependent on CA⁺⁺ ions, protein kinase C and the Na (+) – H + exchange system. Additionally when there is lowered glucose in the brain leading to cerebral global transient ischemia, monoamine release especially dopamine is inhibited. In this regard, Trugman and James [27] showed D1 antagonists lowered glucose utilization by 24–28% in the globus pallidus, entopeduncular nucleus, subthalamic nucleus, substantia nigra, and even the motor cortex, suggesting that stimulation of the D1 receptor by endogenous dopamine contrib-

utes to basal metabolism in these regions. In contrast both D1 and D2 agonists increase glucose utilization. These results suggest that feeding behavior is tied into the stimulation of both D1 and D2 receptors and provides metabolic evidence for the importance of D1 and D2 functional linkage in the brain, which relates to hyperphagia or overeating.

The direct effect of dopamine on glucose release from primary cultured rat hepatocytes were studied in Japan by Shiroyama et al. [28]. In this regard, dopamine is known to induce hyperglycemia in both animals and man. The authors investigated whether dopamine has any direct effect on glucose release from hepatocytes through the glycogenolytic and/or gluconeogenic pathways, and at the same time determined the main type of adrenergic receptor involved in glucose release.

Our hypothesis as well as others, increasing glucose release from tissue would reduce cravings for glucose and carbohydrates. In this regard Shiroyama et al. [28] supported this notion. Glycogen-rich and gluconeogenic-depleted hepatocytes were prepared in order to study glycogenolytic and gluconeogenic-depleted glucose release, respectively. Dopamine caused release of glucose which was inhibited by the beta blocker propranolol. The authors conclude that dopamine has a direct effect on hepatocytes, increasing glucose release via both glycogenolytic and gluconeogenic pathways and mediated by beta adrenergic receptors.

More recently, Hamilton and Freeman [29] studied the effect of glucose on anti-psychotic drug-induced changes in dopamine neuronal activity and suggested that caloric intake may influence antipsychotic drug-induced changes in the population activity of midbrain dopaminergic neurons. In fact, glucose significantly reduced the number of spontaneously active A9 and A10 dopaminergic cells per track in control rats, but significantly attenuated the chronic haloperidol and clozapine-induced reductions in dopaminergic cells per track.

This multi-factorial proposition is supported by the co-morbidities associated with obesity. For example, one-third of all high blood pressure cases are associated with obesity, and obese persons are 50% more likely to have elevated blood cholesterol levels [30]. Adult onset diabetes (Type 2, non-insulin dependent) accounts for nearly 90% of all cases of diabetes. Researchers estimate that 88 to 97% of Type 2 diabetes cases diagnosed in overweight people are a direct result of obesity [31]. Excess weight is an established risk factor for high blood pressure, type 2 diabetes (adult-onset), high blood

cholesterol level, coronary heart disease and gallbladder disease [32].

Pharmaceutical analog: sibutramine HCl, a comparison of its pharmacologic mechanism of action with GenoTrim

Sibutramine HCl (MERIDIA® a registered trademark of Abbott Laboratories) is a FDA-approved pharmaceutical for the treatment of obesity [33]. The major effect of this drug is an anti-craving action derived from its inhibition of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) reuptake. This inhibition of neurotransmitter reuptake increases the length of time 5HT, DA, and NE are available to act in the synaptic junction, and ultimately in an amplification of the neurotransmitter effects to reduce sugar/glucose cravings.

In its simplest form, a component of GenoTrim™ (a trademark of Salugen, Inc.) mirrors sibutramine HCl mechanism and should produce similar anti-craving effects. However, the hypothesis is that DNA-customized GenoTrim, unlike sibutramine HCl, works by answering certain nutrient needs required to silence excessive cravings originating from those systems and delivers the nutrient amounts based upon genetic predisposition. The components of GenoTrim that mimic sibutramine HCl include precursor amino acids DL-phenylalanine and others inhibiting enkephalinase, chromium as a tryptophan enhancing substance, and rhodiola as a suspected inhibitor of catechol-O-methyl transferase (COMT). Thus it is anticipated that the same three neurotransmitters affected by sibutramine HCl could potentially be affected by certain nutraceutical ingredients and may produce similar effects without the noted side effects. It could be hypothesized that by increasing precursor (i.e., phenylalanine, tyrosine, and chromium and or 5-hydroxytryptophane or any other neurotransmitter enhancer even via transport) intake and inhibiting enzymatic degradation by COMT, greater levels of 5HT and DA would be available at the synapse. The availability of certain neurotransmitters at the synapse is also increased since the D-phenylalanine causes preferential release of dopamine via opioid peptide breakdown inhibition. Thus the sum total effect is very similar to sibutramine HCl and the following information will assure the scientific potential of such a novel natural formula.

Most recently, the effects of intravenous sibutramine HCl on brain dopamine and serotonin

flux into striatal and hypothalamic dialysates of freely moving rats was investigated. While low doses of the drug had no effect, higher doses increased both serotonin and dopamine concentrations in the striatal and hypothalamic brain regions. These findings further support the neurochemical effects of sibutramine, and suggest that the drug's anti-obesity action may result from changes it produces in brain dopamine as well as serotonin metabolism [33]. The importance here is that it provides further support for a novel formula containing the aforementioned nutraceutical ingredients that promotes improved body composition via both serotonergic and dopaminergic anti-obesity actions.

Genotrim™

GenoTrim is a DNA-customized nutritional solution for weight management, developed and manufactured by Salugen, Inc., based in San Diego, CA, USA and is under intensive investigation. Based upon an analysis of five genes that potentially influence weight, GenoTrim ingredients and dosages are genetically-guided to address the underlying genetic factors involved in hormones and metabolism that some suggest influence 70% to 80% of overweight cases (ADAM Well-Connected Reports; Weight Control and Diet; Report #53, 02/07/2005). These genes include a serotonin receptor gene 5-HT2a-1438 A > G influencing appetite control, PPAR-Gamma Pro(12)Ala polymorphism influencing fat cell creation and metabolism, Leptin OB gene influencing obesity risk, MTHFR C677T polymorphism influencing folate (vitamin B9) metabolism and homocysteine, and Dopamine D2 Receptor Taq 1 Allele influencing sugar and carbohydrate cravings. By addressing genetic factors that make individuals prone to weight problems, GenoTrim supports healthy sleep, digestion, mood, and fat metabolism which may result in sustainable weight loss and overall trimming. Since Genotrim™ is a DNA-based nutraceutical, it is not possible to provide a standard formula, as it varies based upon the analysis of a person's genes. However, for the purposes of this hypothesis, we provide a discussion about three major ingredients to further explain the data and the concept.

Garcinia cambogia extract and the salts of (–) hydroxycitric acid – potassium and calcium salts of (–) HCA have been shown to effectively blunt the conversion of excess carbohydrate into fat, promote fat oxidation, enhance serotonin release and availability in the brain, promote healthy blood

lipid levels and improve the success of weight management efforts [34].

Passiflora incarnata – Passion flower is a name that has been given to several members of the genus *Passiflora*. There are more than 40 species in the genus whose origins are in both the tropical and subtropical regions of the western hemisphere. Passionflower was first brought to Europe from Mexico in the 16th century by Spanish conquerors. Its main medicinal purpose was that of a calming tea. It is now part of the medicinal herbarium in many countries throughout the world. Passion flower's long history in herbal medicine includes its use as a treatment for colic, diarrhea, dysentery, menstrual pain, skin eruptions, conjunctivitis, hemorrhoids, and muscle spasms. However, the inclusion in any anti-obesity formula also involves its central nervous system effects. Passion flower has demonstrated stress reduction effects. Reducing stress is expected to result in a default lowering of cortisol, reducing the accumulation of excess abdominal fat [35].

Synaptamine™ – A proprietary raw material complex

D-Phenylalanine – Included in synaptamine, *D*-Phenylalanine inhibits enkephalinase, the enzyme that metabolizes or breakdown enkephalins, thereby increasing the availability of enkephalins and presumably, making more dopamine available at the reward sites especially under stressful conditions [36].

L-Phenylalanine – included in synaptamine, *L*-Phenylalanine stimulates the production of dopamine, and/or increases norepinephrine levels in the reward area of the brain. The major problem with this amino acid is that it could compete with other amino-acids such as blood born *L*-tryptophan and *L*-tyrosine at the large neural amino-acid brain carrier system [37]. However, other data demonstrate for the first time that the synthesis and release responses to some dopaminergic agents may be elicited from synaptosomal dopamine, which is formed by the hydroxylation of phenylalanine. Amphetamine and Cogentin increased the release of dopamine formed from ¹⁴C-phenylalanine in rat caudate nucleus synaptosomal preparation and concomitantly stimulated the synthesis. Amfelic acid also caused a net release of that dopamine. In conclusion, the results suggest that synaptosomal particles represent a unit capable of synthesizing dopamine from *L*-phenylalanine and that synthesis from this precursor may be under the regulatory control of the particles [37].

Early clinical results on genotrim™

Several studies have been completed to demonstrate the safety and efficacy of GenoTrim. In the T.R.I.M. Study (genotrim formulation treatment results in improved metrics of weight loss), a path analysis, a well-known statistical regression model, relying on Tau correlation matrix, was used and suggested that two major paths towards weight loss originate with stress reduction. First, there is one leading from reduction in stress through improved sleep, heightened energy, and positive focus to improved performance — and the second leading from reduction in stress through improved appetite, improved weight, and improved inches to well being.

Examination of the data indicates a number of very interesting correlations (both negative and positive): Stress is negatively correlated with sleep ($r = -0.49$), whereby when stress is high sleep is low; stress is positively correlated with appetite ($r = 0.42$), whereby when stress is high appetite is high; stress is negatively correlated with energy ($r = -0.24$) whereby when stress is high energy is low; sleep is positively correlated with energy ($r = 0.44$), whereby when sleep is high energy is high; stress is negatively correlated with wellbeing ($r = -0.36$), when stress is high wellbeing is low; sleep is positively correlated with performance ($r = 0.40$), whereby when sleep is high performance is high; appetite is negatively correlated with focus ($r = -0.30$), whereby when appetite is high focus is low; appetite is positively correlated with weight ($r = 0.21$), whereby when appetite is high weight is high; and finally weight is positively correlated with inches ($r = 0.63$), whereby when weight is high so are inches [38].

A second study of 901 subjects entitled, "Dopamine D2 receptor gene polymorphisms are significantly associated with percentage body fat and obesity in the D.I.E.T. Study: a functional basis for the nutrigenomic response of chromium picolinate (CrP) in producing body composition effects," early findings suggested the need to genotype obese subjects for the "Sweet Tooth Gene" (dopamine (DA) receptor gene) prior to chromium picolinate nutritional supplementation as a treatment modality resulting in weight loss.

In this multi-centered study, a total of 901 subjects were genotyped for the A1 and A2 allele. A total of 257 subjects were assessed for weight, BMI (kg/m^2) and percent body fat using dual energy X-ray absorptiometry (DEXA). The remaining 644 subjects were part of the D.I.E.T. study and were assessed using a questionnaire. In the first popula-

tion, the A1 allele was present in 67% of the obese subjects compared to 3.3 % of the well-screened controls A and 33.3 % for controls B. These differences were significant: Controls A vs. Obese subjects: ($r_2 = 39.6$, $df = 1$, p value less than 0.0001), and Controls B vs. Obese subjects ($r_2 = 25.9$, $df = 1$, p value less than 0.0001). In terms of the role of dopamine in global obesity, the A1 allele was present in 37% of the self identified obese subjects in the D.I.E.T. study. Compared to literature controls ($N = 3,329$), a significant association was found ($\chi^2_2 = 14.47$; $df = 1$, p value less than 0.0001, $OR = 1.407$, 95% CI) [39].

Our hypothesis

We hypothesize that aberrant sugar craving behavior may in part be due to an inadequate dopaminergic activity in the reward center of the brain [40]. This concept was first defined in our paper on reward deficiency syndrome (RDS) [4] in 1996. Over the years this concept has received slow but continued worldwide scientific support. This genetic predisposition drives individuals to engage in activities of behavioral excess, which will increase brain dopamine function. Consuming large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulate the brain's production of and utilization of dopamine [41]. So too does the intake of illicit substances such as crack/cocaine and the abuse of nicotine. Like these other behaviors that were first thought to be treated with behavioral modification alone, obesity is still often times characterized as a behavioral problem. We hypothesize that this inadequate dopaminergic activity is linked to glucose metabolism and obesity. By understanding these biological and genetic factors influencing obesity, we propose that a DNA-customized nutritional regimen may be a critical component to obesity treatment. We propose that along with appropriate behavioral modifications, genetic and biologic factors must be treated to achieve effective and sustainable health improvements leading to optimal weight, and a reduction of obesity and its associated comorbidities. The role of RDS and obesity, along with GenoTrim and DNA-customized nutritional solutions [42] will be the subject of further intensive investigation obtaining support from certain animal studies [43]. With this hypothesis, it is the intention of the study authors to further the discussion around factors influencing obesity beyond behavioral modifications and to elucidate the role of many genes in the obesity epidemic [44]. By proposing a genetic influence on obesity,

the study authors do not reduce or eliminate the impact of appropriate diet, exercise, and other behaviors on promoting healthy weight, but rather we wish to stimulate a discussion that is demonstrated by the data suggesting that weight is hereditary and behavioral modification alone has not reduced the prevalence of this serious chronic disease.

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