Generally, obese and overweight individuals display higher free fatty acid levels, which stimulate insulin resistance. The combination of overweight or obesity with insulin resistance can trigger Type 2 diabetes mellitus (T2DM) and are primary contributing factors to the development of uncontrolled T2DM. Genetic polymorphisms also play an important role as they can impact a population’s susceptibility to becoming overweight or obese and developing related chronic complications, such as uncontrolled T2DM. This review specifically examines the genetic polymorphisms associated with overweight and obesity in patients with uncontrolled T2DM. Particularly, gene polymorphisms in ADIPOQ (rs1501299 and rs17300539), LepR (rs1137101 and rs1045895), IRS2 (rs1805092), GRB14 (rs10195252 and rs3923113) and PPARG (rs1801282) have been associated with overweight and obesity in uncontrolled T2DM.

First draft submitted: 3 December 2015; Accepted for publication: 9 February 2016; Published online: 21 March 2016

Keywords: ADIPOQ • genetic polymorphisms • GRB14 • insulin resistance • IRS2 • LEPR • obesity • overweight • PPARG • uncontrolled T2DM

Background
The WHO [1] defines being overweight as having a BMI equal to or greater than 25 kg/m² and obesity as a BMI equal to or greater than 30 kg/m². BMI, calculated by weight (kg)/height (m²), is used as a measure of weight standards [1]. Being overweight or obese is a risk factor that contributes to Type 2 diabetes mellitus (T2DM) incidence [2,3]. According to the Lancet 2014, Malaysia was rated as the highest of obese country in southeast Asia with heavyweight 45.3% of its population, followed by South Korea (33.2%) and Pakistan (30.7%) [4]. The Malaysian National Health and Morbidity Survey in 2011 indicated that obesity prevalence in Malaysians aged 18 and above had increased from 4.4% in 1996 to 14.2% in 2006 and 15.1% in 2011 [5]. Furthermore, according to WHO statistics in 2014, more than 1.9 billion adults (18 years and older) worldwide were overweight and 600 million were obese respectively [6]. Adipose tissue, which modulates metabolism in obesity, increases the release of nonesterified fatty acids. Nonesterified fatty acids induce insulin resistance and impair β-cell function. β-cell dysfunction exists in individuals who are at high risk of developing T2DM and may be associated with obesity [7].

T2DM is one of the most prevalent conditions in Malaysia. The National Health and Morbidity Survey reported in 2011 that diabetes prevalence was 15.2% (2.6 million Malaysians aged 18 and above) [5] and International Diabetes Federation reported in 2014 that 3.2 million cases diabetes in Malaysia and the prevalence increased to 16.6% [8]. Globally, statistics indicated a prevalence of 6.4%, or approximately 285 million patients had been diagnosed with diabetes in 2010. By 2030, the prevalence is estimated to reach 7.7%, resulting in approximately 439 million patients with T2DM [9]. T2DM is one of...
the most common chronic diseases and is often associated with obesity, hypertension, hyperlipidemia and cardiovascular disease, which are collectively termed ‘metabolic syndrome’ [10]. T2DM is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia related to diabetes causes uncontrolled T2DM leading to long-term damage, dysfunction and failure of various organs, including the kidneys, eyes, heart and blood vessels [10]. Uncontrolled T2DM may also cause acute life-threatening conditions, such as ketoacidosis or nonketotic hyperosmolar syndrome [11]. Management of uncontrolled T2DM has become challenging, because the disease is increasingly complex and, to some extent, controversial. With a widening array of pharmacological agents available, there have been mounting concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycemic control [12]. Additionally, uncontrolled T2DM is linked with obesity that rich in fats. Obesity is a known risk factor for diabetes and induces insulin resistance, which leads to hyperinsulinemia, a compensatory response to insulin resistance [13]. The management of uncontrolled T2DM is also important to decrease obesity severity [14].

Genetic factors are proposed to contribute to the pathogenesis of the disease, and polymorphisms in related genes play important roles in the associated disease risk [15,16]. Genetic factors can be identified through a candidate gene approach in which polymorphisms in associated genes that impact disease susceptibility are detected [17]. Genetic polymorphisms are currently estimated to account for 40–70% of the variance in human adiposity [18]. Genetic polymorphisms are defined as a genetic variant at a single location within a gene, and the variation must be present in at least 1% of a population [19]. In addition, most candidate polymorphism studies rely on prior scientific evidence indicating that the set of polymorphisms is associated or relevant to the disease trait. That is, a SNP is used as a predictor to determine whether a given set of SNPs influences the disease trait and the association with the disease [20]. An SNP, or a single base pair change across the general population at a frequency of at least 1%, is one of most common types of genetic polymorphisms [21]. An SNP can be replaced by insertion of additional sequences or by deletion in the range of one to several thousand base pairs [22]. Finding on the set of SNPs in candidate polymorphisms could provide a better understanding of the genetic basis of diseases. There has already been significant progress in understanding the genetics of T2DM; however, the association of genetic polymorphisms with overweight and obesity in uncontrolled T2DM is not fully understood [23,24]. Therefore, this review investigates the effects of potential genes and their association with overweight and obesity in patients with uncontrolled T2DM. Thus, it may provide novel insights for glycemic control and the improvement of overweight or obesity management in uncontrolled T2DM.

**Identifying the potentially relevant genetic polymorphisms associated with overweight & obesity in uncontrolled T2DM**

Identifying candidate gene polymorphisms is useful to identify genes involved in human disease. According to Kathryn et al., polymorphisms occur throughout the human genome on average once every 500–1000 base pairs [25]. Polymorphisms that are found on the same chromosome are frequently associated with each other [26]. Some genetic polymorphisms are silent with no effect on gene products but are still useful as genetic markers in disease association studies [25]. In order to identify genetic variants of associated risk diseases, there are two main approaches; genome wide association studies (GWAS) and candidate gene approach [22]. GWAS was able to scan in thousands of SNPs to determine certain associated diseases in huge number of populations [27]. Though there is considerable enthusiasm for this approach, according to Weiss et al. the number SNPs needed for such a scan remains controversial and has been suggested as the unpredictable nature of genetic linkage that may make difficult in finding real association [28]. In contrast, candidate gene polymorphisms in association studies have a number of advantages, including directly focusing on a single gene, and frequently looking directly at significant polymorphisms, concerns about to detect relevant association [22]. That is, the goal of candidate gene polymorphism studies is to determine whether a given SNPs or set of SNPs influences the disease of trait directly [19]. Interestingly, from Cathy et al. studies, in order to identify risk variant the massive increase in scale of GWAS, however, has allowed the identification of common genetic variants associated with risk disease that significantly to test candidate gene for risk of disease [29]. In addition, from other studies also revealed that candidate gene studies serve to validate finding from GWAS as well as further explore the risk factors for complex diseases, clinical and biological interaction [19].

The process for selecting candidate gene polymorphisms is depicted in Figure 1. The identification of candidate gene polymorphisms begins with identifying risk variants and candidate SNPs associated with uncontrolled T2DM, overweight and obesity [30]. This is followed by the selection of a putative candidate gene based on its relevance to the mechanism of the disease
Genetic polymorphisms

Review

being investigated [31]. Polymorphisms, typically SNPs, are then assessed and selected based on whether they have a functional consequence on protein products or gene regulation [26]. Targeted genotyping of the candidate SNPs is performed, and susceptibility genes are validated [32]. Finally, the gene variant is verified for disease (trait) association by performing functional studies [26]. Each of the roles of candidate polymorphisms is evaluated for its role in disease mechanism and association with disease prognosis [33].

Figure 1. Flowchart for selecting candidate gene polymorphisms associated with disease.

T2DM: Type 2 diabetes mellitus.
Although a number of studies have reported association of functional or position candidates, only a few genes have been potentially associated with uncontrolled T2DM in overweight or obese patients. In this review article, we discussing several genes that have been identified as susceptibility genes associated with overweight and obesity in uncontrolled T2DM that is ADIPOQ, LEPR, IRS2, GRB14 and PPARG. From previous studies, all these five genes have been implicated using the candidate gene approach [34,35].

Candidate genes associated with overweight & obesity in uncontrolled T2DM

In this review, we also identify the relationship between the polymorphisms in genes, including ADIPOQ, LEPR, PPARG, GRB14 and IRS2, and overweight and obesity in patients with uncontrolled T2DM. A summary of the relationship between genetic factors and overweight and obesity in patients with uncontrolled T2DM is displayed in Figure 2.

Adiponectin (ADIPOQ)

Studies of adipocytes have increased as a result of the rising diabetes and obesity incidences worldwide [36]. ADIPOQ has been identified as a susceptibility locus for metabolic syndrome and T2DM. It is located on chromosome 3q27 and contains three exons that span 17 kb [37]. Antonopoulos et al. reported that adiponectin, which is secreted by the adipose tissue, stimulated the secretion of a variety of secretory proteins involved in the pathogenesis of diabetes and obesity [38]. Adipose tissue also plays multiple, important roles in body weight regulation. Adipocytes store fat in the form of triglycerides and release free fatty acids [39]. Adiponectin is the primary adipocyte secretory protein found in human plasma with roles in muscle and liver insulin sensitivity and glucose tolerance regulation [40]. In particular, adiponectin impacts both oral glucose tolerance and HbA1C. Adiponectin levels are decreased in several metabolic disorders, including obesity, insulin resistance and T2DM [41]. Recent findings also suggested that adiponectin levels in patients with T2DM are more associated with obesity [42] compared with patients without diabetes. Adiponectin has a strong genetic component with heritability between 30 and 50% [43]. Genetic studies on ADIPOQ variants in South Asia emphasize the importance of its relationship with diabetes and obesity. Asian Indians have a unique phenotype characterized by increased abdominal obesity, insulin resistance and hyperglycemia, which result in increased susceptibility to uncontrolled T2DM [44]. Adiponectin is one of the primary adipocyte secretory proteins with potent roles in insulin sensitivity in the muscle and liver by regulating glucose tolerance [45]. Currently, ADIPOQ gene polymorphisms have been implicated in T2DM, hyperglycemia and impaired insulin action risk [46]; however, association studies, particularly those concerning in uncontrolled T2DM with overweight and obesity, are still unclear.

Leptin receptor (LEPR)

Leptin is a peptide hormone that is primarily secreted by white adipose tissue [47]. Leptin regulates body weight and plays important roles in the modulation of glucose and lipid metabolism and glycemia [48]. Leptin, an adipocyte-derived hormone, plays a crucial role in body weight regulation, mediated by interaction with its specific leptin receptor (LEPR) [49]. Leptin controls energy balance and food intake through LepR in the hypothalamus of the brain, which suggests that LEPR polymorphisms may contribute to obesity or obesity-related diseases [50]. LEPR is found on chromosome 1p31, contains 20 exons and spans approximately 100 kb [51]. The absence of LEPR leads to uncontrolled eating and increased body fat mass [52]. LEPR was reported to have a profound impact on body weight, insulin resistance and metabolic disease parameters [53]. In addition, Zhang et al. found that LEPR regulates body weight, lipid metabolism, blood pressure homeostasis and T2DM [51].

Additionally, Gulturk et al. indicated that leptin can regulate lipid homeostasis independent of body weight changes [54]. Das et al. concluded that leptin is a novel marker for overweight and obesity because overweight and obesity, primarily central obesity, may lead to insulin resistance and thereby T2DM [55]. Furthermore, LEPR genes have been investigated in the search for gene variants linking obesity, T2DM and its associated complications [56]. Pankov identified functional LEPR mutations that lead to the production of a shorter receptor, which resulted in obesity and diabetes [57]. In addition, LEPR plays a role in glucose metabolism [58]. For example, Gilberto et al. revealed that leptin exerts insulin- and glucose-lowering effects by enhancing insulin sensitivity and glucose uptake [59]. Moreover, LEPR is present in pancreatic β-cells and could therefore modulate glucose-induced insulin secretion, chronic hyperglycemia and uncontrolled T2DM [60]. Genetic variation at the LEPR locus has been suggested to play a significant role in T2DM and the pathophysiology of human obesity [61].

Growth factor receptor-bound protein 14 (GRB14)

The GRB proteins constitute a family of structurally-related multi domain adapters with diverse cellular functions. GRB14, in particular, has been implicated
GRB14 has also been implicated as a novel candidate gene associated with obesity and T2DM. The GRB14 gene, which encodes the GRB14 adapter protein, interacts with tyrosine kinase receptors and attenuates insulin action. GRB14 is highly expressed in liver, skeletal muscles and pancreas and is located at chromosome 2. Additionally, GRB14 is expressed in adipose tissue. A study by Junhui et al. demonstrated that GRB14 expression was increased in subcutaneous adipose tissue of obese humans but decreased in the liver. In the present study, GRB14 modulated hyperglycemia in the pancreas, liver, skeletal muscle and blood of individuals with T2DM. Furthermore, GRB14 was identified as a genetic locus associated with T2DM in people of south Asian ancestry.

Peroxisome proliferator-activated receptor gamma (PPARG)

PPARs regulate the expression of genes involved in lipid and glucose metabolism. There are three PPAR genes: PPARα, PPARγ and PPARδ. The three genes are distinguished from each other by their cellular activation, including activation by fatty acids and derivatives, and tissue distribution. PPARγ is an adipose tissue-specific nuclear hormone receptor that regulates adipocytes. The gene encoding PPARγ is a candidate for T2DM and obesity susceptibility, because PPARγ is implicated in adipocyte differentiation and glucose homeostasis. Shin et al. reported no significant association of PPARδ polymorphisms with T2DM risk or BMI. In contrast, Marillia et al. indicated that PPARγ was associated with body weight, obesity and several metabolic syndrome traits, including BMI, total cholesterol, glucose concentration and diastolic blood pressure. In addition, PPARγ is located at the chromosome 3p25 region of the genome and has 11 exon. PPARγ was also significantly associated with higher fasting glucose levels. Mattevi et al. indicated that PPARγ polymorphisms contributed to higher BMIs in adult males. Additionally, Gouda et al. identified PPARγ as a strong candidate gene for T2DM.

Figure 2. Summary of genetic factors associated with overweight and obesity in patients with uncontrolled T2DM.

T2DM: Type 2 diabetes mellitus.
PPARG is involved in adipocyte differentiation and lipid storage and is highly expressed in the liver, skeletal muscle and kidney where it regulates fatty acid catabolism, glucose metabolism and insulin sensitivity [75]. PPARG plays a fundamental role in adipogenesis and insulin sensitivity and, therefore, is a potential candidate gene for insulin resistance and T2DM [76]. Radha et al. identified PPARG as one of the primary candidate genes associated with adipogenesis, insulin resistance and T2DM [77]. Maya et al. observed that PPARG contribution to the genetic risk of T2DM, especially in obese subjects, worsened insulin resistance and increased fasting insulin levels [72]. Moreover, Barroso et al. found that several genetic variations in the human PPARG gene were associated with insulin resistance, obesity and T2DM [78].

Insulin receptor substrate 2 (IRS2)
Insulin receptor substrate (IRS) is a hormone insulin that is an intermediate in insulin signaling and is essential for glucose and lipid metabolism and basic cell growth function [79]. IRS1 and IRS2 are responsible for skeletal muscle and adipose tissue glucose uptake, glucose production by the liver and insulin production in pancreatic β-cells [80]. IRS2 plays an important role in insulin signaling, and in humans, IRS2 polymorphisms were associated with lower T2DM risk in lean individuals but greater risk in obese individuals [81]. IRS2 interacts with body weight in the pathogenesis of T2DM [82]. Overweight individuals with the IRS2 polymorphism appear to be at higher risk of developing T2DM [82]. A study on Caucasians in Italy found that the IRS2 polymorphism conveys a low risk of diabetes to lean individuals compared with that of obese subjects [82]. In addition, according to Clausen et al., IRS2 is also involved in the interaction between obesity and insulin resistance [83]. Furthermore, IRS2 is located at chromosome 13q34 and has two exons [84].

From previous findings, ADIPOQ, Lepr, PPARG, GRB14 and IRS2 were identified as a strong genetic marker that associated with obesity and T2DM [41, 42, 50, 51, 60, 63, 68, 72, 74, 81, 82]. Nevertheless, there are still limited studies on the association of genetic polymorphisms with overweight and obesity in uncontrolled T2DM [23, 24].

Relationship between AdipoQ, Lepr, Grb14, PPARG & IRS2 polymorphisms & overweight & obesity in uncontrolled T2DM
Overweight and obesity are often related to T2DM and can cause uncontrolled T2DM if patients do not control glycemia and insulin resistance [11, 85]. This is because, according to Kahn et al., T2DM is characterized by a combination of disturbances in insulin secretion by pancreatic β cells and peripheral insulin resistance, with obesity being an independent risk factor for T2DM. Many common variants and polymorphisms in genes, including ADIPOQ, Lepr, GRB14, PPARG and IRS2, have been studied for their risk and possible role as determinants for the association of overweight and obesity with T2DM; however, studies have generally not analyzed patients with uncontrolled T2DM. Five gene polymorphisms and eight SNPs are summarized in Table 1 with their parameter associations with overweight, obesity and T2DM and have high potential to influenced and associated with uncontrolled T2DM.

Li et al. reported that the ADIPOQ rs1501299 polymorphism was associated with T2DM in a Chinese population [108]. Melistas et al. found that rs1501299 with a conversion of G > T was associated with higher fasting insulin levels and possibly associated with body fat [89]. Bebe-Dimmer et al. and Bouatia-Naji et al. observed that the presence of the T allele corresponded with severe obesity [86, 90], while Hara et al. determined that the GG genotype was associated with T2DM, higher insulin resistance and lower adiponectin levels in subjects with higher BMIs [87]. In another study by Huang et al., the T allele was strongly associated with central obesity and hyperglycemia [88]. Previously, Ramya et al. also found that adiponectin gene variants contributed to the risk of developing T2DM, obesity and hyperlipidemia in a South Indian population [44]. In addition, Fumeron et al. indicated that ADIPOQ rs17300539 was associated with T2DM, with the GA genotype conferring an increased risk of hyperglycemia in patients with T2DM [92]. The A allele in rs17300539 also conferred a higher T2DM risk in obese French–Caucasians [93]. In a European population, adiponectin levels were found to be higher in subjects carrying the A allele; however, the SNP was associated with obesity and HOMA-IR [91]. Conversion of the G allele to the A allele conferred a favorable increase on circulating adiponectin levels [94]. From these results, it is clear that the ADIPOQ gene had a higher association with T2DM and increased BMI; however, the association with uncontrolled T2DM is not fully understood, particularly in Malaysian populations.

LEPR polymorphisms contribute to common forms of human obesity. Duarte et al. found that the LEPR Q223R variant was related to a 58% increase in obesity risk [99]. Murugesan et al. demonstrated that the Q223R polymorphism was associated with obesity, fat mass and T2DM [95]. In addition, Bourmaiza et al. indicated that the LEPR polymorphism was associated with metabolic syndrome and obesity risk in Tunisian subjects. The GG/GG genotype was associated with an increased obesity risk in patients with T2DM compared with that of controls [109]. The rs1137101 SNP resulting in a
Table 1. SNPs associated with overweight and obesity in individuals with uncontrolled Type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP ID</th>
<th>Position</th>
<th>Parameter association</th>
<th>Population</th>
<th>Sample size (N)</th>
<th>p-value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdipoQ</td>
<td>rs1501299</td>
<td>+26 G &gt; T</td>
<td>T allele associated with obesity</td>
<td>African–American</td>
<td>475</td>
<td>–</td>
<td>[86]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG associated with T2DM, higher insulin resistance and higher BMI</td>
<td>Japanese</td>
<td>864</td>
<td>0.01</td>
<td>[87]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T allele associated with obesity and hyperglycaemia</td>
<td>Indigenous Taiwanese</td>
<td>550</td>
<td>–</td>
<td>[88]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T allele associated with higher fasting insulin levels and higher HOMA-IR score, possible association with body fat</td>
<td>Greek women</td>
<td>379</td>
<td>–</td>
<td>[89]</td>
</tr>
<tr>
<td></td>
<td>rs17300539</td>
<td>-139 G &gt; A</td>
<td>T allele associated with severe obesity but not adiponectin level</td>
<td>French–Caucasians (obese/lean)</td>
<td>2579</td>
<td>0.006</td>
<td>[90]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A allele associated with higher adiponectin levels, higher BMI and obesity</td>
<td>Europian origin</td>
<td>1852</td>
<td>0.015</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA carriers had increased risks for becoming hyperglycaemic</td>
<td>French–Caucasians</td>
<td>4500</td>
<td>0.005</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A allele associated with higher risk of T2DM in obese subjects</td>
<td>French–Caucasians (obese/lean)</td>
<td>1375</td>
<td>0.003</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A allele associated with higher adiponectin levels</td>
<td>African–American</td>
<td>1196</td>
<td>0.002</td>
<td>[94]</td>
</tr>
<tr>
<td>LepR</td>
<td>rs1137101</td>
<td>A &gt; G</td>
<td>G allele associated with increased rates of obesity, higher BMI and fast mass</td>
<td>Coimbatore</td>
<td>300</td>
<td>–</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G allele associated with increased BMI, higher leptin levels and insulin</td>
<td>Caucasians</td>
<td>–</td>
<td>–</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A allele associated with higher insulin, leptin levels and body fat</td>
<td>Mexican</td>
<td>103</td>
<td>0.001</td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>rs1045895</td>
<td></td>
<td>AA genotype had greater risk of developing T2DM</td>
<td>Finnish</td>
<td>507</td>
<td>0.042</td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G &gt; C</td>
<td>G allele associated with higher fasting glucose and fasting insulin</td>
<td>Belgian</td>
<td>280</td>
<td>–</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>Q223R</td>
<td>A &gt; G</td>
<td>G allele associated with higher leptin levels and may related to obesity risk</td>
<td>Brazil</td>
<td>350</td>
<td>0.007</td>
<td>[99]</td>
</tr>
<tr>
<td></td>
<td>rs1045895</td>
<td></td>
<td>Q223R polymorphisms associated with obesity, fat mass and T2DM</td>
<td>Coimbatore</td>
<td>300</td>
<td>–</td>
<td>[95]</td>
</tr>
</tbody>
</table>

HOMA-IR: HOMA insulin resistance; T2DM: Type 2 diabetes mellitus; WHR: Waist to hip ratio.
Table 1. SNPs associated with overweight and obesity in individuals with uncontrolled Type 2 diabetes mellitus (cont.).

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP ID</th>
<th>Position</th>
<th>Population</th>
<th>Sample size (N)</th>
<th>p-value</th>
<th>Ref.</th>
<th>Parameter association</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRB14</td>
<td>rs10195252</td>
<td>T &gt; C</td>
<td>European</td>
<td>917</td>
<td>-</td>
<td>[65]</td>
<td>T allele associated with increased body weight</td>
</tr>
<tr>
<td></td>
<td>rs322113</td>
<td>C &gt; A</td>
<td>European</td>
<td>5561</td>
<td>-</td>
<td>[69]</td>
<td>A allele associated with higher BMI and WHR</td>
</tr>
<tr>
<td></td>
<td>rs10195252</td>
<td>T &gt; C</td>
<td>South Asian</td>
<td>77167</td>
<td>0.0003</td>
<td>[69]</td>
<td>A allele associated with higher BMI and WHR</td>
</tr>
<tr>
<td>PPARG</td>
<td>rs1801282</td>
<td>(Pro12Ala)</td>
<td>Tunisian</td>
<td>575</td>
<td>-</td>
<td>[101]</td>
<td>Ala allele associated with greater insulin sensitivity and BMI</td>
</tr>
<tr>
<td></td>
<td>rs1801282</td>
<td>(Pro12Ala)</td>
<td>Caucasians</td>
<td>3250</td>
<td>-</td>
<td>[102]</td>
<td>CC and GG genotype associated with higher BMI and WHR</td>
</tr>
<tr>
<td></td>
<td>rs1801282</td>
<td>(Pro12Ala)</td>
<td>Italians</td>
<td>674</td>
<td>-</td>
<td>[104]</td>
<td>CC and GG genotype associated with a higher BMI in obese individuals</td>
</tr>
<tr>
<td></td>
<td>rs1801282</td>
<td>(Pro12Ala)</td>
<td>Turkish</td>
<td>3080</td>
<td>0.002</td>
<td>[105]</td>
<td>CC and GG genotype had a higher risk to overweight</td>
</tr>
<tr>
<td></td>
<td>rs1801282</td>
<td>(Pro12Ala)</td>
<td>Taiwanese</td>
<td>674</td>
<td>0.017</td>
<td>[105]</td>
<td>CC and GG genotype had a higher risk to overweight</td>
</tr>
</tbody>
</table>

A nucleotide change from A > G was primarily associated with increased adiposity, BMI and percent fat mass, as well as higher insulin and leptin levels [53]. Other studies have also found the G allele to be primarily associated with increased obesity rates, BMI and as well as higher leptin levels [95]. Additionally, higher fasting glucose and fasting insulin levels have been associated with the G allele compared with the C allele [110]. Conversely, Guizar-Mendoza et al. found that the A allele was associated with increased leptin levels, body fat and higher insulin levels and subsequent T2DM risk [98]. This finding was supported by Salopuro et al. who found that the AA genotype also conferred a greater risk of developing T2DM [96]. Other studies have reported that the LepR rs1045895 polymorphism was associated with changes in BMI over time [97]. Moreover, two studies by Liu et al. and Wauters et al. reported that the K656N G>C SNP was associated with increased fat mass, and the C allele has been linked to higher fasting glucose and insulin levels and increased fat mass [100,101]. Noriko et al. observed that in obese patients with T2DM there was a positive correlation with the leptin to adiponectin ratio, while Yadav et al. found that adiponectin and leptin may correlate with BMI [111,112]. Specifically, leptin in subcutaneous adipose tissue was positively correlated with a BMI >27 kg/m², while adiponectin was positively correlated with high-density lipoprotein-cholesterol [112]. However, the association of these polymorphisms with overweight and obesity in uncontrolled T2DM is still controversial and warrants further research.

Meirhaeghe et al. indicated that the PPARG rs1801282 SNP significantly predicted overweight, higher BMI and total cholesterol [101]. Altshuler et al. demonstrated that P12A significantly (p = 0.02) decreased diabetes risk [104]. Ben Ali et al. observed that the Ala/Ala genotype was significantly associated with a higher BMI in obese subjects compared with that of control subjects in a Tunisian population [102]. The Ala allele was also strongly associated with greater insulin sensitivity and BMI [103]. In addition, the PPARG Ala allele was associated with increased leptin levels in a Mexican–American population and correlated with LepR polymorphisms [113]. Sanghera et al. found that the PPARG rs1801282 polymorphism was associated with two AdipoQ polymorphisms and the effect on T2DM development and overweight risk in an Asian Indian Sikh population but not in obese individuals. PPARG maps to chromosome 3p24 and has been implicated in several genome-wide linkage analyses for T2DM, insulin resistance and obesity [114]. Hsiao et al. observed that the CC and GG genotypes were associated with a higher overweight risk in a Taiwanese population [109]. PPARG was positively associated with T2D in obese individuals [115]. Hara et al. reported that AdipoQ maps to chromosome 3q27 and is implicated in
T2D [87], while Menzaghi et al. found that Adipoq was implicated in both T2DM and obesity [116]. However, the role of PPARγ in T2DM, obesity and insulin resistance is currently unknown in Northern Indians [69] and has not been reported in studies investigating individuals with uncontrolled T2DM.

A SNP in GRB14 also correlated with the PPARγ gene and was associated with higher insulin sensitivity and pancreatic β-cell function. Jaspal et al. investigated the SNP in adipose tissues, liver and other tissues and found that it was associated with T2DM mediated through adiposity, as overweight and obesity are major risk factors for T2DM [68]. Junhui et al. demonstrated that the rs10195252 T allele was associated with increased subcutaneous fat in obese humans and increased body weight [63]. According to Heid et al., at chromosome 2q24, the GRB14 gene polymorphisms, rs3923113 and rs10195252 were associated with central adiposity and increased GRB14 expression in adipose tissue and reported associated in fat distribution study [66]. Schleinitz et al. indicated that GRB14 is located within ±1 Mb of rs10195252, and the T allele of rs10195252 is associated with increased subcutaneous adipose tissue GRB14 expression [117]. Furthermore, from previous studies also indicate that the GRB14 polymorphism is the most strongly associated with T2DM [66,68].

Other studies have reported that the G1057D variant of the IRS gene was associated with overweight and T2DM [82]. The GD genotype was associated with a lower T2DM prevalence in control subjects but a higher prevalence in overweight patients. This finding suggests that the DD and GD genotypes might be negatively associated with T2DM in individuals with lower BMIs but positively associated with T2DM in overweight individuals. From Mammarella et al. studies also demonstrates that overweight acted as a modifier for T2DM risk, as the combination of the GD and DD genotypes were associated with an increased T2DM risk [82]. Furthermore, Bodhini et al. observed that the IRS2 (G1057D) polymorphism was associated with T2DM and obesity in an Asian–Indian population [106]. The DD genotype at position 1057 conferred increased susceptibility to T2DM with an odds ratio of 2.19; and the GG and GD genotypes showed among the obese subjects [106]. Moreover, according to Radha et al., the DD genotype in IRS2 also has been increased by interacting with obesity [77]. Sevim et al. also found that D1057D allele increased the risk of diabetes among obese individual in Turkish population [107]. In addition, the Asp1057 allele in IRS2 was more prevalent in Pima Indians compared with the Caucasian population, in which the Gly1057 allele is predominant. Consistent with this, Pima Indians have much higher obesity prevalence than that of the Caucasian population [81]. Stefan et al. found that obesity affects the expression of the subset of genes related to glucose metabolism and insulin resistance that enhance IRS2 expression, which possibly contributes to insulin resistance and T2DM development and alters fat tissue [118].

All the eight SNPs rs1501299, rs17300539, rs1137101, rs1045895, rs1805092, rs3923113 and rs1801282 revealed a positive correlation with higher BMI and increased obe-

### Executive summary

#### Genetic factors associated with disease

- Genetic factors, such as polymorphisms, can greatly impact an individual’s susceptibility to becoming overweight or obese and developing related chronic complications, such as uncontrolled Type 2 diabetes mellitus (T2DM). Currently, studies are focusing on the genetics of T2DM and obesity; however, the genetic factors associated with overweight or obesity in uncontrolled T2DM are not fully understood. Thus, future studies with larger sample sizes are needed to investigate the association with uncontrolled T2DM, because they may present a new perspective for studying the impact of such gene polymorphisms in human populations. These studies will also provide significant insight into the roles of polymorphisms associated with overweight and obesity in uncontrolled T2DM specifically.

#### Indicating the potential gene polymorphisms

- To identify genetic polymorphisms in a potential candidate gene for obesity, overweight and uncontrolled T2DM, all the possible variants and candidate SNPs were verified based on their functional sequences and the relevance in the mechanism of the associated disease. The eight SNPs identified rs1501299, rs17300539, rs1137101, rs1045895, rs1805092, rs10195252, rs3923113 and rs1801282, have great potential to associate with overweight and obesity and thus influence uncontrolled T2DM.

#### Possible association of gene polymorphisms with overweight & obesity in uncontrolled T2DM

- Data from previous studies have indicated that gene polymorphisms of AdipoQ (rs1501299 and rs17300539), Lepr (rs1137101 and rs1045895), IRS2 (rs1805092), GRB14 (rs10195252 and rs3923113) and PPARγ (rs1801282) are associated with T2DM, overweight and obesity. Adipoq polymorphisms have the potential to correlate with PPARγ rs19801282 in associated diseases (trait). Lepr and PPARγ polymorphisms have a great impact on body weight and insulin resistance. In addition, the GRB14 polymorphisms rs10195252 and rs3923113 are correlated with each other.
sity risks that can trigger T2DM hence, contributing in uncontrolled T2DM development [63, 68, 77, 88, 97, 101, 103, 112].

**Conclusion**

From this review, ADIPOQ (rs1501299, rs17300539), LepR (rs1137101, rs1045895), GRB14 (rs10195252, rs3923113), PPARG (rs1801282) and IRS2 (1805092) were identified as a strong genetic polymorphisms that associated with obesity and potentially trigger to uncontrolled T2DM.

**Future perspective**

The findings in this association study could provide an opportunity to better understand the roles and impact of each gene polymorphism in associated diseases and promote improved approaches to manage overweight or obesity in individuals with uncontrolled T2DM. Hence, these findings may serve as novel insights to control glycemia and reduce insulin resistance progression. Furthermore, this will help clinicians screen patients earlier, thus preventing serious consequences.

**Author contributions**

Nor Briah Kasim wrote the paper. Hasniza Zaman Huri, Shireen Ratna Vethakkam, Bashar Mudhaffar Abdullah and Luqman Ibrahim revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

**Financial & competing interests disclosure**

The authors would like to thank the University of Malaya Research Grant (RP024C-14HTM) for financial and technical support. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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