

1 **Title: Genetic Polymorphisms of the Endocannabinoid System in Obesity and Diabetes**

2 **Short title: Endocannabinoid polymorphisms in obesity and diabetes**

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10 **Key words: Polymorphisms, endocannabinoid, diabetes, obesity, cannabinoid**

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12 Word count: 1,788

13

14 **Abbreviations**

15 **2-AG:** 2-arachidonoyl glycerol

16 **BMI:** Body mass index

17 **CB1:** Cannabinoid receptor 1

18 **CB2:** Cannabinoid receptor 2

19 **CRP:** C-reactive protein

20 **DAGL:** Diacylglycerol lipase

21 **ECS:** Endocannabinoid system

22 **FAAH:** Fatty acid amide hydrolase

23 **HDL-C:** High density lipoprotein cholesterol

24 **HOMA<sub>IR</sub>:** Homeostatic Model Assessment for Insulin Resistance

25 **IL-6:** Interleukin-6

26 **LDL-C:** Low density lipoprotein cholesterol

27 **NAPE-PLD:** N-acyl phosphatidylethanolamine phospholipase D

28 **MAGL:** Monoacylglycerol lipase

29 **MetS:** Metabolic syndrome

30 **SNP:** Single nucleotide polymorphism

31 **TGs:** Triglycerides

32 **TNF $\alpha$ :** Tumour necrosis factor alpha

33 **T2DM:** Type 2 Diabetes Mellitus

34 **WC:** Waist circumference

35 **WHR:** Waist-to-hip ratio

36 **Abstract**

37 The endocannabinoid system (ECS) is involved in many physiological processes including fertility,  
38 pain and energy regulation. The aim of this systematic review was to examine the contribution of  
39 single nucleotide polymorphisms (SNPs) of the ECS to adiposity and glucose metabolism.  
40 Database searches returned 734 articles, of which 65 were included covering 70 SNPs in genes  
41 coding for cannabinoid receptors 1 and 2 (CB<sub>1</sub>, CB<sub>2</sub>), fatty acid amide hydrolase (FAAH) and N-  
42 acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). No studies included SNPs relating  
43 to monoacylglycerol lipase or diacylglycerol lipase. The CB<sub>1</sub> receptor SNP rs1049353 showed 17  
44 associations with lower body mass index (BMI) and fat mass (5 studies). It also showed 3  
45 associations with lower insulin levels (1 study). Conversely, the CB<sub>1</sub> receptor SNP rs806368 was  
46 associated with increased BMI and waist circumference (2 studies). The FAAH SNP rs324420 as  
47 associated with increased obesity (3 studies). A haplotype of NAPE-PLD was associated with  
48 decreased BMI (1 study). 60 SNPs showed no association with any measured outcome. This  
49 review suggests a complex but important role of ECS SNPs in energy and glucose metabolism.

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51 **Introduction**

52 The endocannabinoid system (ECS) consists of two G-protein coupled receptors (CB<sub>1</sub> and CB<sub>2</sub>)  
53 and endogenously produced ligands (or endocannabinoids, such as anandamide and 2-  
54 arachidonoyl glycerol) and the enzymes involved in their synthesis or degradation; fatty acid  
55 amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), diacylglycerol lipase (DAGL) and N-acyl  
56 phosphatidylethanolamine phospholipase D (NAPE-PLD). It is well established that CB<sub>1</sub> activation  
57 leads to increases in energy storage<sup>1</sup> which occurs via increased motivation to consume food  
58 and decreased satiety.

59

60 Single nucleotide polymorphisms (SNPs) are naturally occurring variations of a genetic sequence,  
61 which often affect protein structure. To date, studies on the effects of endocannabinoid SNPs  
62 have focused on central disorders such as Parkinson's disease and Alzheimer's disease<sup>2</sup>.

63 However, there is accumulating evidence for the role of endocannabinoid SNPs in adiposity<sup>3</sup> and  
64 glucose metabolism<sup>4</sup>. Therefore, the aim of this systematic review was to systematically collate  
65 the evidence relating to SNPs of the ECS in obese or diabetic phenotypes. By studying amino acid  
66 sequence alterations and any resultant residue changes, we hoped to identify important genetic  
67 changes which alter the normal physiology of adiposity and glucose metabolism.

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70 **Materials and Methods**

71 Searches were performed using PubMed, EMBASE and Web of Science by two independent  
72 researchers and concluded on 26/1/2018. Additional studies were identified from bibliographies.  
73 The search terms used were: Cannabinoid OR endocannabinoid receptor OR CB<sub>1</sub> OR CB<sub>2</sub> OR FAAH  
74 OR fatty acid amide hydrolase AND polymorphism AND obesity OR diabetes OR BMI OR  
75 monoacylglycerol lipase OR MAGL OR diacylglycerol lipase OR DAGL OR N-acyl  
76 phosphatidylethanolamine-specific phospholipase D OR NAPE PLD. A summary of search results  
77 and exclusions is given in supplemental Figure S1, and a full reference list is available in the  
78 supplementary appendix. The SNP database dbSNP was used to gather information regarding  
79 nucleotide and amino acid changes<sup>5</sup>.

80

81 Articles included were original studies relating to polymorphisms of the ECS affecting energy  
82 regulation, glucose homeostasis and adiposity. Demographic and clinical parameters included  
83 were: body mass index (BMI); waist circumference (WC); waist-to-hip ratio (WHR); body weight;  
84 adiposity; Type II Diabetes Mellitus (T2DM); insulin and glucose levels; Homeostatic Model  
85 Assessment for Insulin Resistance (HOMA<sub>IR</sub>); adipokine levels (adiponectin, leptin, and resistin);  
86 cardiovascular parameters (blood pressure, heart rate); inflammation (levels of interleukin 6 (IL-  
87 6), tumour necrosis factor alpha (TNF $\alpha$ ) and C-reactive protein (CRP)); and lipid levels  
88 (triglycerides, HDL-C and LDL-C). Records excluded were review articles, articles on the ECS not  
89 relating to polymorphisms, studies regarding central disorders, non-human studies and studies in  
90 a language other than English.

91

92 Included articles were analysed for significant ( $p < 0.05$ ) positive or negative associations between  
93 SNPs and relevant parameters. A 'positive' association refers to there being a higher value of the  
94 measured outcome in the presence of the polymorphism, whereas 'negative' refers to there  
95 being a lower value in the presence of the polymorphism. A lack of significant association

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96 between the measured outcome and the polymorphism is described as a 'neutral' association.

97 Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias <sup>6</sup>.

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## 100 **Results**

101 65 studies were identified from 733 full-text articles. Risk of bias of these studies was overall low  
102 and is summarised in supplemental Figure S2. In total, 38 CB<sub>1</sub>, 18 CB<sub>2</sub>, 13 FAAH and 1 NAPE-PLD  
103 SNPs were studied. No studies relating to MAGL or DAGL SNPs were found. The most commonly  
104 studied SNPs and those which showed the most significant associations were CB<sub>1</sub> SNPs  
105 rs1049353 and rs806368, and FAAH SNP rs324420. Their associations with body weight and  
106 glucose metabolism parameters are presented in Table 1. All SNPs and their associations with  
107 measured outcomes are documented in supplementary Table S1. A summary of all included  
108 studies and their relevant findings is shown in supplementary Table S2.

109

### 110 **BMI and body weight**

#### 111 **CB<sub>1</sub>**

112 The rs1049353 mutant allele was associated with lower BMI in six European populations  
113 <sup>7,8,9,10,11,12</sup> and decreased fat mass in a Danish population (n=783) <sup>13</sup>. Conversely, homozygosity  
114 for the rs1049353 mutant allele was associated with higher WHR and WC in obese men (p<0.01,  
115 n=1,064) <sup>14</sup>, and increased childhood obesity in a European population (p=0.01, n=200) <sup>15</sup>. The  
116 majority of associations with rs1049353 were neutral (90%) (Table 1). However, negative  
117 associations were more common than positive (Figure 1), suggesting this SNP plays a part in a  
118 more complex genetic susceptibility to increase adiposity. Male carriers of the rs806368 mutant  
119 allele showed greater BMI values in a Japanese cohort (p=0.001), and were more likely to be  
120 obese (p=0.01, n=1,452) <sup>16</sup> (Table S1).

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#### 122 **FAAH**

123 FAAH polymorphism rs324420 was positively associated with obesity in four cohorts (n=18,987)  
124 <sup>17,18,19,20</sup>.

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126 **CB<sub>2</sub>**

127 The mutant allele of CB<sub>2</sub> SNP rs3123554 was associated with lower total body fat in females but  
128 not males in a European cohort (p=0.001), with lower BMI in subjects at risk of T2DM (p<0.01)  
129 and reduced weight loss (p<0.01, n=2,006) <sup>21</sup>.

130

131 **NAPE-PLD**

132 In a Norwegian cohort, a haplotype of NAPE-PLD showed an association with increased BMI  
133 (p<0.05, n=5,011) <sup>22</sup>.

134

135 **Type II Diabetes**

136 **CB<sub>1</sub>**

137 The mutant allele of CB<sub>1</sub> polymorphism rs1049353 was associated with lower insulin, glucose and  
138 HOMA<sub>IR</sub> levels in Spanish obese women <sup>29</sup> and lower insulin in two other European cohorts  
139 (n=983) <sup>23,24</sup>. CB<sub>1</sub> SNP rs806365 was associated with decreased HOMA<sub>IR</sub> values and incidence of  
140 T2DM in a North American cohort (p=<0.05, n=2,411) <sup>25</sup>.

141

142 **CB<sub>2</sub>**

143 The mutant allele of CB<sub>2</sub> polymorphism rs3123554 was associated with raised insulin levels and  
144 HOMA<sub>IR</sub> values in an obese population (n=1,027) <sup>26</sup> (Figure 1).

145

146 **FAAH**

147 The mutant allele of FAAH polymorphism rs324420 was associated with lower insulin levels in  
148 two obese populations (p<0.05, n=165) <sup>27,28</sup>. rs324420 was also associated with lower HOMA<sub>IR</sub>  
149 levels in obese Spanish females (p<0.05, n=143) <sup>28</sup>.

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151 **Lipids**



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152 Overall, 22 positive associations with lipid levels were seen. The mutant allele of CB<sub>1</sub> SNP  
153 rs1049353 was associated with higher HDL and lower TGs in three cohorts<sup>29,30,31</sup>, as well as lower  
154 TGs in two populations (n=808)<sup>9,29</sup> (Table 1).

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156 FAAH SNPs rs324420 and rs3123554 were associated with higher TG levels in European cohorts  
157 (p<0.05, n=1,644)<sup>26,30</sup> (Table 1). FAAH SNP rs324420 was also associated with raised anandamide  
158 levels in a Brazilian population (p<0.05, n=200).<sup>42</sup>

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161 **Discussion**

162 The aim of this study was to collate evidence relating to SNPs of the ECS and obese or diabetic  
163 phenotypes to identify important genetic changes which alter metabolism. From the 65 included  
164 articles, 70 polymorphisms were studied. CB<sub>1</sub> SNP rs1049353 showed 17 associations with lower  
165 BMI and fat mass. It also showed associations with reduced glucose, insulin and HOMA<sub>IR</sub> values.  
166 CB<sub>1</sub> polymorphism rs806368 showed 5 associations with increases in BMI, WC and WHR. The  
167 FAAH SNP rs324420 showed 7 associations with increased incidence of obesity. 60 SNPs showed  
168 no association with any measured outcome. These findings suggest an important role of selected  
169 SNPs of the ECS in adiposity, although the number of studies showing no associations means that  
170 their contribution is likely part of complex interactions.

171

172 The SNP rs1049353 occurs at nucleotide position 1359, a region of the CB<sub>1</sub> (CNR1) gene coding  
173 for the receptor's intracellular domain or C-terminal. One study showed that replacement of the  
174 C-terminal resulted in decreased affinity of the CB<sub>1</sub> agonist CP55940 and increased affinity of the  
175 CB<sub>1</sub> antagonist SR141716A<sup>33</sup>. This suggests that the C-terminal is important in receptor  
176 signalling. Although rs1049353 is a synonymous SNP and does not result in an amino acid residue  
177 change (Thr>Thr), altered substrate interaction deriving from synonymous SNPs has been  
178 observed elsewhere<sup>34</sup> suggesting this is a legitimate theory.

179

180 The literature showed 13 associations between rs1049353 and reductions in parameters of  
181 glucose metabolism<sup>9,10,12,14,22,23,24,29,30,39,45,46,48</sup> (Figure 1). This suggests that that this SNP is important  
182 in diabetic phenotypes, likely caused by upregulation of gluconeogenic transcription factors due  
183 to increased CB<sub>1</sub> receptor activity. It is unclear why many studies (n=14) showed no association  
184 with parameters of glucose metabolism.

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186 The rs324420 SNP reduces FAAH activity and increases likelihood for the enzyme itself to be  
187 degraded<sup>41</sup>, leading to cannabinoid overactivity. Subsequent CB<sub>1</sub> activation leads to adipogenesis  
188 and reduced expenditure, all of which contribute to obesity-related phenotypes. Our analysis  
189 showed that rs324420 was associated with higher anandamide levels<sup>42</sup>, increased BMI and  
190 obesity<sup>17,18,32</sup>, which suggests cannabinoid over-activation and subsequent adiposity and that  
191 this SNP therefore reduces FAAH activity (Table 1).

192

193 The potential contribution of CNR2 polymorphisms to human metabolism is less clear. Fewer  
194 studies investigated these SNPs, and the two polymorphisms studied (rs3123554 and  
195 rs35761398) showed conflicting associations with body weight parameters and glucose  
196 metabolism. As CB<sub>2</sub> receptors are found primarily in the central nervous system and on immune  
197 cells, it is likely that they are less involved in the regulation of body fat and therefore any  
198 alterations in their genetic structure are less relevant here. As no studies were found relating to  
199 SNPs of DAGL or MAGL, their contribution to obesity and glucose metabolism remains unclear.

200

201 Increasing age may determine the impact of the polymorphism. For instance, associations  
202 between SNPs rs2023239 and rs806381 and increased anthropometric measurements were  
203 found only in adult subjects<sup>35,36</sup>. Ageing leads to reductions in ligand binding<sup>37</sup> and coupling  
204 between the CB<sub>1</sub> receptor and its G-protein<sup>38</sup>, which may account for the delayed onset of  
205 increases in body weight parameters in some populations. There may also be an impact of  
206 gender in these data. Male carriers of the mutant alleles of CNR1 polymorphisms rs1049353 and  
207 rs806368 have an increased likelihood of obesity<sup>14,16</sup>. Similarly, the associations between the  
208 CNR2 polymorphism rs3123554 and lower BMI, weight and body fat percentage were reported in  
209 female subjects<sup>21</sup>. Gender differences in feeding behaviour have been previously observed in  
210 animal models<sup>39</sup>. This may be explained by the action of oestrogen, which uncouples CB  
211 receptors from their effector systems in synaptic terminals, reducing the effect of cannabinoids

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212 <sup>40</sup>. Higher oestrogen levels in non-pregnant females may therefore contribute to these gender-  
213 specific findings.

214

215 In conclusion, associations between the mutant allele of the CB<sub>1</sub> SNP rs1049353 and decreased  
216 fat mass, weight and BMI indicate that this SNP is an important contributor to alterations in  
217 metabolism. Evidence points to decreased receptor functionality affecting normal pathways of  
218 adipogenesis and energy regulation. Its effects also extend to improvements in lipid levels and  
219 parameters of glucose metabolism. The mutant allele of FAAH polymorphism rs324420 was  
220 associated with increased BMI and triglyceride levels, possibly caused by decreased enzyme  
221 activity and overactivation of the ECS. Other SNPs had varying associations but often presented  
222 conflicting results. These findings represent therapeutic targets for the management of obesity  
223 and hyperlipidaemia, and assessment of patients for these genetic changes would provide an  
224 opportunity to give personalised treatment for a proportion of patients. Further studies in  
225 populations of varying demographics are needed to investigate the role that other SNPs play in  
226 adiposity and glucose metabolism, as well as genetic studies to determine the molecular changes  
227 of SNPs responsible for alterations in function.

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#### 229 **Declaration of interest**

230 There is no conflict of interest that could be perceived as prejudicing the impartiality of the  
231 research reported.

232

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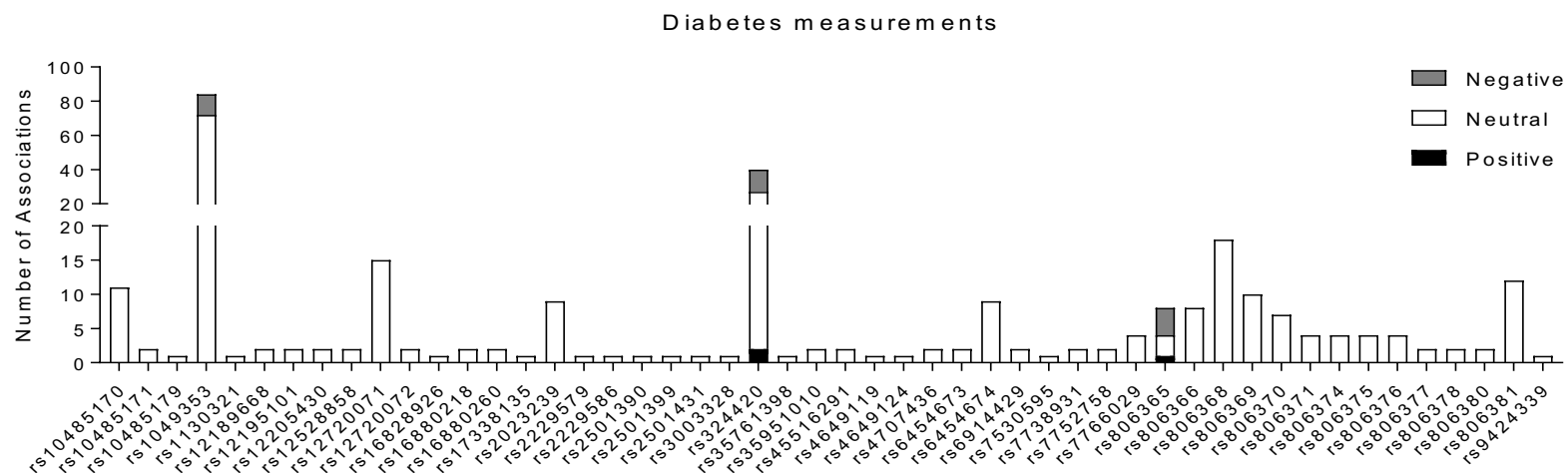
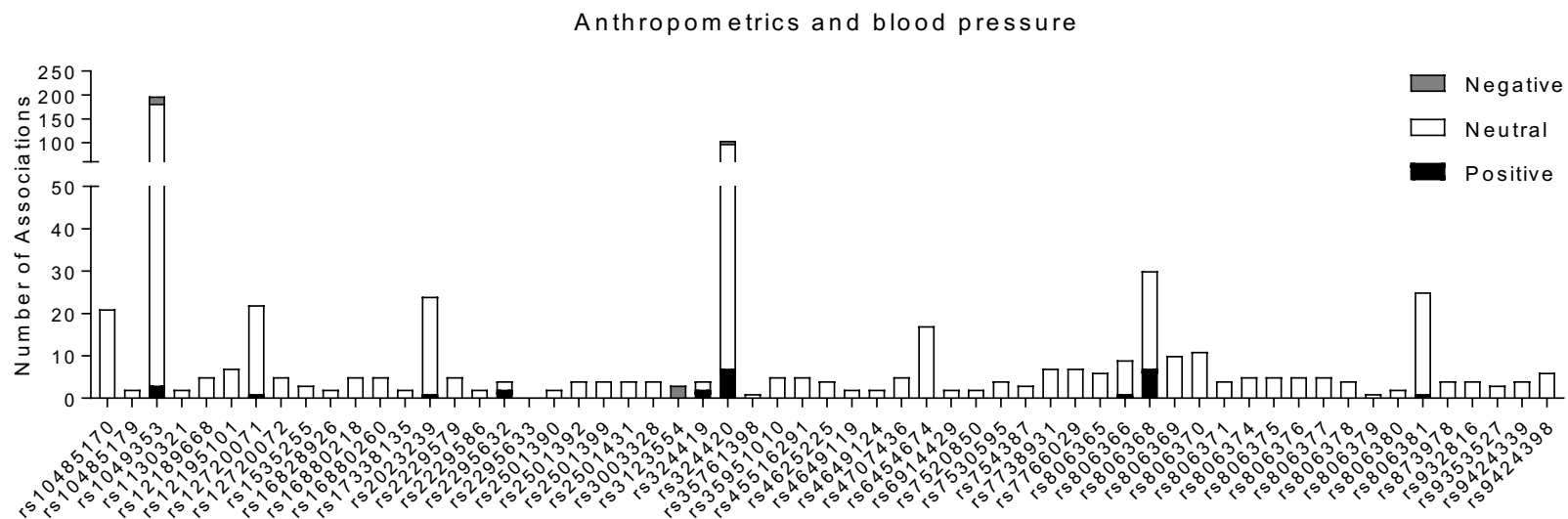
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292 For full list of references, please refer to the Appendix section online.

**Table 1.** Associations found between single nucleotide polymorphisms and metabolic and anthropometric parameters.

Polymorphism	Gene	Nucleotide change	Nucleotide position	Region of gene	Amino acid change	Amino acid position	Associations
rs1049353	CNR1	G>A	1359	Exon	Thr>Thr	453	<p><b>Positive:</b></p> <ul style="list-style-type: none"> <li>• Homozygosity for mutant allele associated with increased WHR and WC in obese men only.<sup>14</sup></li> <li>• Mutant allele associated with higher fat in post-menopausal women.<sup>43</sup></li> <li>• Mutant allele associated with increased BMI in T2DM subjects.<sup>44</sup></li> <li>• Wild-type allele associated with higher HOMA<sub>IR</sub>.<sup>45</sup></li> <li>• Mutant allele group associated with greater weight loss and decrease in BMI.<sup>46</sup></li> <li>• Mutant allele associated with childhood obesity.<sup>47</sup></li> </ul> <p><b>Negative:</b></p> <ul style="list-style-type: none"> <li>• Mutant allele associated with lower glucose.<sup>46</sup></li> <li>• Mutant allele associated with lower insulin.<sup>22,39,48</sup></li> <li>• Mutant allele with lower BMI.<sup>10,11,12,14,31</sup></li> <li>• Mutant allele with lower HOMA<sub>IR</sub>, TGs.<sup>9,10,12,14,23,24,29,30</sup></li> </ul>
rs806368	CNR1	T>C	4895	Intron	-	-	<p><b>Positive:</b></p> <ul style="list-style-type: none"> <li>• Mutant allele associated with increased WHR.<sup>47</sup></li> <li>• Mutant allele associated with increased TGs.<sup>49</sup></li> <li>• Mutant allele associated with increased BMI, WC and obesity.<sup>16</sup></li> </ul>
rs324420	FAAH	C>A	385	Exon	Pro>Thr	129	<p><b>Positive:</b></p> <ul style="list-style-type: none"> <li>• Mutant allele associated with higher insulin and HOMA<sub>IR</sub> in patients without MetS.<sup>50</sup></li> <li>• Homozygosity for mutant allele associated with increased BMI.<sup>17</sup></li> <li>• Mutant allele associated with obesity.<sup>19,20</sup></li> <li>• Wild-type allele associated with childhood obesity.<sup>51</sup></li> <li>• Mutant allele associated with increased TGs.<sup>32</sup></li> </ul> <p><b>Negative:</b></p> <ul style="list-style-type: none"> <li>• Mutant allele associated with lower TGs, glucose and HOMA<sub>IR</sub> levels.<sup>28,44</sup></li> <li>• Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.<sup>52</sup></li> <li>• Lower insulin and HOMA<sub>IR</sub> in mutant-type group. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, HOMA<sub>IR</sub> and TGs.<sup>27</sup></li> <li>• Wild-type allele associated with lower WC, BMI, HOMA<sub>IR</sub> and TGs in subjects with MetS.<sup>53</sup></li> <li>• Mutant allele associated with lower insulin, glucose and HOMA<sub>IR</sub> values.<sup>54</sup></li> </ul>

Abbreviations: CNR1, cannabinoid receptor gene 1; FAAH, fatty acid amide hydrolase; WC, waist circumference; WHR, waist-to-hip ratio; BMI, body mass index; TGs, triglycerides; HOMA<sub>IR</sub>, homeostatic model assessment of insulin resistance; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ ; MetS, metabolic syndrome; T2DM, Type 2 Diabetes Mellitus.



**Figure 1.** Number of associations found between ECS polymorphisms and anthropometric and diabetic parameters.



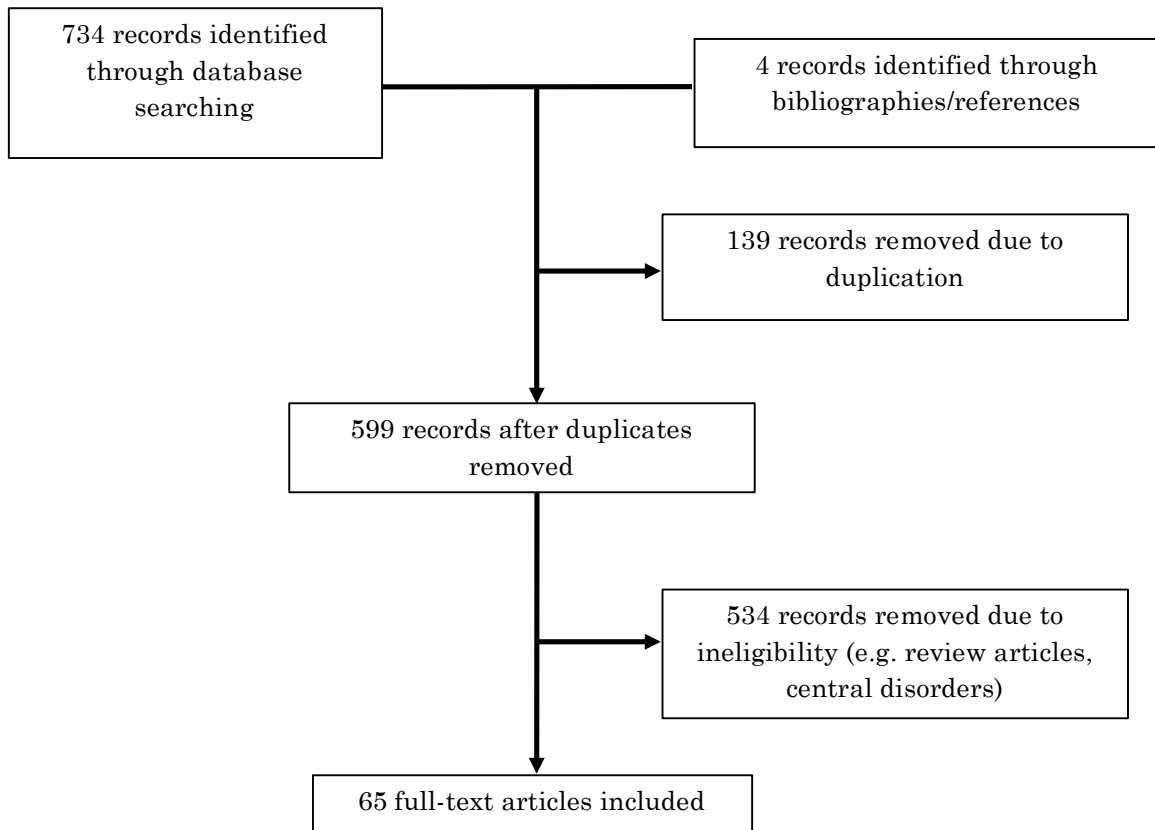


Figure S1: Summary of search results and exclusions

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Aberle J., et al 2008	o	o	-	+	+	+	o
Aberle J., et al 2007	o	o	-	+	o	+	o
Aller et al. 2012	o	o	+	+	o	+	o
Baye T., et al 2008	+	o	+	+	o	+	o
Bellini G., et al 2015	+	o	+	+	o	+	o
Benzinou M., et al 2008	+	o	+	+	+	o	+
Bordicchia M., et al 2010	o	o	+	+	+	+	+
Buraczynska M., et al 2014	o	o	+	o	o	o	+
Caruso M., et al 2012	+	o	+	+	o	o	o
Chmelikova M., et al 2014	+	o	+	+	+	+	+
Col Araz N., et al 2012	+	o	+	o	+	o	o
de Luis D., et al 2009	o	o	+	o	+	+	+
de Luis D., et al 2010a	o	o	+	+	+	+	+
de Luis D., et al 2010b	+	o	+	+	+	+	o
de Luis D., et al 2010c	+	o	+	+	+	+	+
de Luis D., et al 2010d	+	o	+	+	+	+	o
de Luis D., et al 2011a	+	o	-	-	+	+	+
de Luis D., et al 2011b	o	o	+	+	+	+	o
de Luis D., et al 2011c	+	o	+	+	+	+	o
de Luis D., et al 2011d	o	o	+	+	+	o	o
de Luis D., et al 2011e	o	o	-	+	+	o	o
de Luis D., et al 2012	+	o	+	+	+	o	o
de Luis D., et al 2013	+	o	-	-	+	o	o
de Luis D., et al 2014	+	o	+	o	+	o	o
de Luis D., et al 2015a	+	o	-	-	+	+	o
de Luis D., et al 2015b	+	o	+	+	+	o	o
de Luis D., et al 2015c	+	o	+	+	+	o	o
de Luis D., et al 2017	+	o	+	+	+	o	+
de Miguel-Yanes J., et al 2011	o	o	+	o	+	+	o
Dinu I., et al 2009	o	o	+	+	+	+	o
Durand E., et al 2008	o	o	+	o	+	+	o
Feng Q., et al 2010	o	o	+	o	+	+	o
Feng Q., et al 2013	o	o	+	+	+	+	o
Frost M., et al 2010	+	o	+	+	+	+	o
Gazzerro P., et al 2007	o	o	+	o	+	+	o
Grolmusz VK., et al 2013	+	o	+	o	+	+	+
Hu W., et al 2010	+	o	+	+	+	+	o
Jaeger JP., et al 2008	+	o	o	o	+	+	o
Jensen DP., et al 2007	+	o	+	+	+	+	+
Ketterer C., et al 2014	o	o	+	+	+	+	+
Knoll N., et al 2012	+	o	+	+	+	o	o
Laczmanski L., et al 2011	o	o	+	o	+	+	+
Lenarcik-Kabza A., et al 2014	+	o	+	o	+	+	+
Lieb W., et al 2009	o	o	+	+	+	+	+
Liu R., et al 2011	o	o	+	+	o	o	+
Martins C., et al 2015	o	o	o	o	+	+	o
Milewicz A., et al 2010	o	o	+	+	+	+	+
Monteleone P., et al 2008	o	o	+	o	+	+	+
Muller TD., et al 2007	+	o	+	+	+	+	+
Muller TD., et al 2010	+	o	o	+	+	+	o
Mutombo PB., et al 2011	o	o	+	+	+	+	+
Papazoglou D., et al 2008	o	o	-	+	+	+	+
Peeters A., et al 2007	o	o	+	+	+	o	o
Reinhard W., et al 1998	+	o	+	+	+	+	+
Russo P., et al 2007	o	o	o	o	+	+	o
Schleinitz D., et al 2010	o	o	+	+	+	+	+
Sipe JC., et al 2005	+	o	+	+	+	+	+
Suarez-Pinilla P., et al 2015	o	o	-	+	o	o	+
Tiwari et al., 2010	o	o	+	+	o	o	+
Vazquez-Roque M., et al 2011	+	o	+	+	+	o	+
Wang L., et al 2003	+	o	+	+	+	+	+
Wang R., et al 2012	+	o	+	+	+	o	+
Wangensteen T., et al 2010	o	o	o	+	+	o	o
Zhang Y., et al 2009	+	o	-	+	+	+	o
Zhuang M., et al 2012	o	o	o	+	+	+	o

Figure S2: Results of Risk of Bias assessment for included studies



**Table S1.** Associations found between single nucleotide polymorphisms and metabolic and anthropometric parameters.

Polymorphism	Gene	Nucleotide change	Nucleotide position	Region of gene	Amino acid change	Amino acid position	Associations
rs10485170	CNR1	A>G	-	-	-	-	<p><b>Neutral:</b></p> <ul style="list-style-type: none"> <li>No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMA<sub>IR</sub>).<sup>82</sup></li> <li>No association with anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index) in postmenopausal women.<sup>43,91</sup></li> <li>No association with antipsychotic-induced weight gain.<sup>92</sup></li> </ul> <p><b>Positive:</b></p> <ul style="list-style-type: none"> <li>Homozygosity for mutant allele associated with increased WHR and WC in obese men only.<sup>14</sup></li> <li>Mutant allele associated with higher android fat deposit and percentage of android fat in postmenopausal women.<sup>43</sup></li> <li>Mutant allele associated with increased BMI in T2DM subjects.<sup>74</sup></li> <li>Mutant allele associated with higher adiponectin and visfatin levels. Wild-type group had higher HOMA<sub>IR</sub>, TNF<math>\alpha</math> and resistin.<sup>66</sup></li> <li>Mutant allele associated with higher adiponectin levels.<sup>75</sup></li> <li>After 3 months' diet, mutant allele group associated with greater weight loss, decrease in BMI, and decrease in LDL.<sup>81</sup></li> <li>Homozygosity for mutant allele associated with increased cholesterol levels.<sup>80</sup></li> <li>Mutant allele associated with childhood obesity.<sup>15</sup></li> <li>Mutant allele associated with higher HDL-C.<sup>29,10</sup></li> <li>Mutant allele associated with lack of decrease in leptin following hypocaloric diet.<sup>76</sup></li> </ul>
rs1049353	CNR1	G>A	1359	Exon	Thr>Thr	453	<p><b>Neutral:</b></p> <ul style="list-style-type: none"> <li>No association with BMI.<sup>16,35,64,69</sup></li> <li>No association with BMI, weight, WC, WHR, glucose, total cholesterol, LDL, HDL, TG, IL-6, or leptin.<sup>66,81</sup></li> <li>No association with BMI, cholesterol, LDL-C, HDL-C.<sup>85</sup></li> <li>No association with TC, HDL-C, LDL-C.<sup>24</sup></li> <li>No association with anthropometric parameters (BMI, weight, fat free mass (kg), fat mass (kg), WC, WHR, SBP, DBP, RMR).<sup>23,30,47,49</sup></li> <li>No association with anthropometric parameters (BMI, weight, fat free mass (kg), fat mass (kg), WC, WHR, SBP, DBP, RMR), dietary intake (energy (kcal/day), carbohydrates (g/day), fat (g/day), protein (g/day)) and exercise (hrs/week) or adipocytokines ((IL-6), TNF-<math>\alpha</math>, adiponectin, resistin, leptin).<sup>29,46,68,71,84</sup></li> <li>No associations with total body fat mass, BMI, WHR, abdominal and femoral subcutaneous fat mass or any biochemical markers (n=7).<sup>13</sup></li> <li>No association with glucose, total cholesterol, LDL-C, HDL-C, TGs, lipoprotein (a), insulin, HOMA<sub>IR</sub> CRP.<sup>8</sup></li> <li>No association with BMI, weight, fat mass, WC, WHR, SBP, DBP, glucose, LDL-C, TC, insulin or HOMA<sub>IR</sub>.<sup>31</sup></li> <li>No association with T2DM.<sup>74</sup></li> </ul>

								<ul style="list-style-type: none"> <li>No association with glucose, TC, LDL-C, HDL-C, TGs, lipoprotein (a), insulin, HOMA<sub>IR</sub>, CRP.<sup>46,68</sup></li> <li>No association with glucose, TC, LDL-C, CRP, lipoprotein (a).<sup>29</sup></li> <li>No association with glucose, TC, LDL-C, insulin, HOMA<sub>IR</sub>, CRP, dietary intake.<sup>30</sup></li> <li>No association with SBP, DBP, TC, HDL-C or LDL-C.<sup>9</sup></li> <li>No difference between basal and post-diet anthropometric measurements or cardiovascular risk factors.<sup>76</sup></li> <li>No difference in decrease in BMI, weight, fat mass, fat free mass, WC, WHR, SBP, DBP, glucose, HDL-C, TGs or insulin between wild- or mutant-type group following treatment with liraglutide.<sup>8</sup></li> <li>No association with carbohydrate, fat, m-fat, p-fat, protein or fibre intake.<sup>31</sup></li> </ul> <p><b>Negative:</b></p> <ul style="list-style-type: none"> <li>Mutant allele associated with lower glucose.<sup>81</sup></li> <li>Mutant allele with lower BMI.<sup>10,11</sup></li> <li>Mutant allele with lower HOMA<sub>IR</sub>, TGs.<sup>10</sup></li> <li>Mutant allele associated with lower weight, BMI, fat mass<sup>8</sup>, WC, insulin, HOMA<sub>IR</sub> and CRP.<sup>24</sup></li> <li>Mutant allele associated with lower BMI, SBP, HOMA<sub>IR</sub> and CRP and higher HDL-C.<sup>12</sup> Lack of improvement in cholesterol, glucose, insulin, TGs, HOMA<sub>IR</sub> and leptin compared with wild-type group following hypocaloric diet.<sup>84</sup></li> <li>Mutant allele with lower TGs, insulin and HOMA<sub>IR</sub> values.<sup>29</sup></li> <li>Mutant allele with decreased resistin, leptin and IL-6 following weight loss.<sup>46</sup></li> <li>Mutant allele with decreased glucose, insulin, HOMA<sub>IR</sub> and incidence of MetS.<sup>23</sup></li> <li>Mutant allele with better improvements in HOMA<sub>IR</sub> following treatment with liraglutide.<sup>8</sup></li> <li>Mutant allele with lower TGs and higher HDL-C.<sup>30</sup></li> <li>Mutant-type group associated with lower TGs and higher HDL-C, and lower cholesterol and saturated fat intake.<sup>31</sup></li> <li>Mutant allele with decreased dietary cholesterol and saturated fats.<sup>93</sup></li> <li>Mutant allele associated with lower BMI, WC, HOMA<sub>IR</sub>, TG levels and prevalence of MetS.<sup>9</sup></li> </ul>
rs12720071	CNR1	A>G	3813	3 Prime Untranslated Region (3' UTR) <sup>44</sup>	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele associated with increased WC and subscapular skinfold thickness.<sup>3</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with anthropometric (weight, height, BMI, WHR, WC) or biochemical (HDL-C, LDL-C, TGs, glucose) measurements.<sup>47,49</sup></li> <li>No association with Anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, FIRI)<sup>8</sup></li> <li>No association with BMI, WC, TC, HDL-C, LDL-C, TGs, glucose, SBP, DBP, MBP.<sup>88</sup></li> <li>No association with impaired glucose metabolism.<sup>73</sup></li> <li>No association with HOMA<sub>IR</sub>, insulin, glucose.<sup>4</sup></li> <li>No associations with BMI, WC or visceral adipose tissue.<sup>64</sup></li> </ul>	
rs2023239	CNR1	C>T	5489	Intron	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele associated with higher BMI.<sup>36</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with obesity.<sup>35,69</sup></li> </ul>	

							<ul style="list-style-type: none"> <li>No association with anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index).<sup>87,91</sup></li> <li>No association with anthropometric measurements (BMI, WC, WHR, SBP, DBP) and biochemical (TC, TGs).<sup>94</sup></li> </ul>
rs6454674	CNR1	G>T	-	-	-	-	<p>Neutral</p> <ul style="list-style-type: none"> <li>No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMA<sub>ir</sub>).<sup>43,82,91</sup></li> </ul>
rs806365	CNR1	C>T	-	-	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele with increased BMI and TGs.<sup>49</sup></li> </ul> <p>Neutral</p> <ul style="list-style-type: none"> <li>No association with glucose.<sup>4</sup></li> <li>No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA<sub>1c</sub>, T2DM).<sup>16</sup></li> <li>No associations with BMI, waist circumference or visceral adipose tissue.<sup>64</sup></li> <li>No association with WC, hip circumference, WHR), insulin responsiveness (insulin, glucose, insulin:glucose, HOMA<sub>ir</sub>), lipids (TC, LDL-C, HDL-C).<sup>49</sup></li> </ul> <p>Negative</p> <ul style="list-style-type: none"> <li>Mutant allele with lower HOMA<sub>ir</sub> and insulin levels.<sup>4</sup></li> </ul>
rs806366	CNR1	T>C	-	-	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Associated with increased BMI and TGs.<sup>49</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with HOMA<sub>ir</sub>, glucose or insulin levels.<sup>4</sup></li> <li>No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA<sub>1c</sub>, T2DM).<sup>16</sup></li> <li>No associations with BMI, waist circumference or visceral adipose tissue.<sup>64</sup></li> </ul>
rs806368	CNR1	T>C	4895	Intron	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele associated with increased WHR.<sup>47</sup></li> <li>Mutant allele associated with increased TGs.<sup>49</sup></li> <li>Mutant allele associated with increased BMI, WC, SBP and obesity.<sup>16</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with weight, height, BMI, WC, HDL-C, LDL-C, TGs, glucose and lifestyle factors (n=3).<sup>47</sup></li> <li>No association with BMI<sup>83</sup>, WC, subscapular skinfold thickness.<sup>3</sup></li> <li>No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMA<sub>ir</sub>).<sup>43,82</sup></li> <li>No association with HOMA<sub>ir</sub>, glucose, insulin levels.<sup>4</sup></li> <li>No associations with BMI, waist circumference or visceral adipose tissue.<sup>64</sup></li> </ul>
rs806369	CNR1	C>T	-	Intron	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele with increased TGs, TC.<sup>49</sup></li> </ul> <p>Neutral</p> <ul style="list-style-type: none"> <li>No association with BMI.<sup>83</sup></li> </ul>

							<ul style="list-style-type: none"> <li>No association with BMI, WC, hip circumference, WHR, insulin, glucose, insulin:glucose, HOMA<sub>1c</sub>, LDL-C, HDL-C.<sup>16,49</sup></li> <li>No association with association with HOMA<sub>1c</sub>, glucose and insulin levels.<sup>4</sup></li> </ul>
rs806370	CNR1	C>T	-	Intron	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele with raised HDL-C.<sup>49</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with BMI.<sup>35,83</sup></li> <li>No association with BMI, WC, hip circumference, WHR, insulin, glucose, insulin:glucose, HOMA<sub>1c</sub>, TC, LDL-C, TGs.<sup>16,49</sup></li> </ul>
rs806371	CNR1	G>T	-	Intron	-	-	<p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with HOMA<sub>1c</sub>, glucose, insulin levels.<sup>4</sup></li> <li>No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA<sub>1c</sub>, T2DM)<sup>16</sup></li> <li>No associations with BMI, waist circumference or visceral adipose tissue.<sup>64</sup></li> </ul> <p>Negative:</p> <ul style="list-style-type: none"> <li>Mutant allele with lower HDL-C levels.<sup>79</sup></li> </ul>
rs806381	CNR1	A>G	10908	Intron	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele with higher BMI.<sup>36</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMA<sub>1c</sub>).<sup>13,43,82</sup></li> <li>No association with BMI, WC, WHR, SBP, DBP, TC, TGs.<sup>94</sup></li> <li>No association with anthropometric measurements (Weight, BMI, WC, fat (%), android fat deposit, gynoid fat deposit, SBP, DBP) and biochemical measurements (TC, HDL-C, LDL-C, TGs, glucose, insulin, FIRI).<sup>91</sup></li> </ul>
rs10485179	CNR1		-	Intron	-	-	<ul style="list-style-type: none"> <li>No association with obesity-related or glucose metabolism parameters.<sup>13</sup></li> </ul>
rs35761398	CNR2	A>G	188	Exon	Gln>Arg	63	<ul style="list-style-type: none"> <li>No association with BMI, HOMA<sub>1c</sub>, TC, HDL-C or TG levels.<sup>95</sup></li> </ul>
rs3123554	CNR2	G>A	-	-	-	-	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant-type group had higher BMI, weight, fat mass, WC TGs, insulin and HOMA<sub>1c</sub> than wild-type group.<sup>26</sup></li> </ul> <p>Neutral:</p> <ul style="list-style-type: none"> <li>No difference in dietary intake between genotypes.<sup>26</sup></li> </ul> <p>Negative:</p> <ul style="list-style-type: none"> <li>Mutant allele associated with lower BMI, weight and body fat in women. Carriers also lost less weight following lifestyle interventions.<sup>21</sup></li> </ul>
rs324419	FAAH	A>G	895	Exon	Ala>Ala	275	<p>Neutral:</p> <ul style="list-style-type: none"> <li>No association with obesity.<sup>51</sup></li> <li>No association with BMI, waist circumference or visceral adipose tissue.<sup>64</sup></li> </ul>
rs324420	FAAH	C>A	385	Exon	Pro>Thr	129	<p>Positive:</p> <ul style="list-style-type: none"> <li>Mutant allele associated with higher insulin and HOMA<sub>1c</sub> in patients without MetS.<sup>50</sup></li> <li>Homozygosity for mutant allele associated with increased BMI.<sup>17</sup></li> <li>Mutant allele associated with obesity.<sup>19</sup></li> </ul>

- Wild-type allele associated with childhood obesity.<sup>51</sup>
- Wild-type genotype associated with class III adult obesity.<sup>20</sup>
- Mutant allele associated with increased HDL-C.<sup>20</sup>
- Wild-type allele associated with higher HDL-C levels in subjects with MetS.<sup>53</sup>
- Mutant allele associated with increased TGs.<sup>32</sup>

Neutral:

- No association with BMI.<sup>96</sup>
- No differences in cholesterol levels between genotypes.<sup>80</sup>
- No association with anthropometric measurements<sup>18,28</sup> or dietary intake.<sup>28,44</sup>
- No differences in anthropometric, metabolic parameters or adipocytokines between genotypes in MetS or non-MetS subjects.<sup>50</sup>
- No association with BMI, WC, WHR, glucose, insulin, C-peptide, HOMA<sub>IR</sub>, TGs, TC.<sup>72</sup>
- No association with binge-eating disorder.<sup>19</sup>
- No association with child obesity or T2DM.<sup>20</sup>
- No association with BMI, waist circumference or visceral adipose tissue.<sup>64</sup>
- No association with SBP, DBP, TC or LDL-C levels.<sup>53</sup>
- No association with BMI, weight, TC, LDL-C, HDL-C, TGs, glucose, insulin, HOMA<sub>IR</sub>, SBP, DBP.<sup>48</sup>

Negative:

- Mutant allele associated with greater decrease in TGs and total cholesterol following low fat diet.<sup>85</sup>
- Mutant allele associated with lower TGs, glucose, HOMA<sub>IR</sub> and IL-6 levels.<sup>44</sup>
- Mutant allele associated with lower glucose, insulin, HOMA<sub>IR</sub> and visfatin levels.<sup>28</sup>
- Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.<sup>52</sup>
- Lower insulin, HOMA<sub>IR</sub> and CRP in mutant-type group. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, TC, LDL-C, HOMA<sub>IR</sub>, CRP and TGs.<sup>27</sup>
- Mutant allele associated with lower adiponectin levels and higher AEA levels.<sup>42</sup>
- Wild-type allele associated with lower WC, BMI, HOMA<sub>IR</sub> and TGs in subjects with MetS.<sup>53</sup>
- Mutant allele associated with lower insulin, glucose and HOMA<sub>IR</sub> values.<sup>54</sup>
- Mutant allele associated with reduced levels of HDL-C.<sup>32</sup>

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Abbreviations: CNR1, cannabinoid receptor gene 1; CNR2, cannabinoid receptor gene 2; FAAH, fatty acid amide hydrolase; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; RMR, resting metabolic rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides; HOMA<sub>IR</sub>, homeostatic mode assessment of insulin resistance; FIRI, fasting insulin resistance index; IL-6, interleukin-6; CRP, C-reactive protein; m-fat, monounsaturated fat; p-fat, polyunsaturated fat; MetS, metabolic syndrome; T2DM, Type 2 Diabetes Mellitus.



**Supplemental Table S2. All included studies and associations with anthropometric and/or blood measurements of adiposity and glucose metabolism**

Study	N	M/F	Population	Endpoint	Polymorphism	Main findings	Association summary
Aller et al. 2012 <sup>66</sup>	71	47/23	NAFLD	Body weight, Insulin resistance, adipokines	rs1049353	No differences for: BMI, weight, WC, WHR, glucose, total cholesterol, LDL, HDL, TG, IL-6, or leptin. Mutant-type group had higher adiponectin and visfatin levels. Wild-type group had higher HOMA <sub>ir</sub> , TNF $\alpha$ and resistin.	Neutral = 11 Positive = 2 Negative = 3
Aberle et al. 2008 <sup>81</sup>	1,721	688/1033	BMI >25 kg/m <sup>2</sup>	Body weight parameters, cholesterol, insulin and glucose	rs1049353	At baseline no differences in weight, BMI, TG, total cholesterol, HDL, LDL. Glucose was higher in wild-type. After 3 months' diet, mutant allele group associated with greater weight loss, decrease in BMI, and decrease in LDL. No differences between groups in change in glucose, TGs, cholesterol or HDL.	Neutral = 10 Negative = 4
Chmelikova et al. 2014 <sup>80</sup>	155	Not reported	Chronic heart failure	Cholesterol	rs1049353 rs324420	Homozygosity for mutant allele was associated with increased cholesterol levels No differences in cholesterol levels between groups	Positive = 1 Neutral = 1
Col Araz et al. 2012 <sup>15</sup>	200		Obese children	BMI	rs1049353	Mutant allele associated with childhood obesity	Positive = 1
de Luis et al. 2009 <sup>24</sup>	66	17/49	Morbidly obese	Anthropometric parameters (n=9), cardiovascular risk factors (n=8) and adipocytokines (n=5).	rs1049353	Mutant allele associated with lower weight, BMI, fat mass, WC, insulin, HOMA <sub>ir</sub> and CRP. No differences detected between groups for other parameters (n=10).	Negative = 7 Neutral = 10
de Luis et al. 2010a <sup>68</sup>	60	14/46	Diabetic	Anthropometric parameters (n=9), cardiovascular risk factors (n=9) dietary intake (n=9) and adipocytokines (n=5).	rs1049353	No association with anthropometric parameters (n=9), cardiovascular risk factors (n=9) dietary intake (n=9) or adipocytokines (n=5).	Neutral = 32
de Luis et al. 2011a <sup>84</sup>	249	56/193	BMI >30 kg/m <sup>2</sup>	Anthropometric parameters (n=10), cardiovascular risk factors (n=8) and adipocytokines (n=5).	rs1049353	No association with basal or post-treatment anthropometric or biochemical variables in either wild- or mutant-type group (n=46) No difference in effect of either diet on anthropometric variables (n=20) No difference in effect of either diet on glucose, TC, insulin and HOMA <sub>ir</sub> values between mutant- or wild-type group. No improvement of mutant-type group in cholesterol, glucose, insulin, TG, HOMA <sub>ir</sub> and leptin values compared with wild-type group following either diet.	Neutral = 74 Negative = 12
de Luis et al. 2011b <sup>29</sup>	290	0/290	BMI >30 kg/m <sup>2</sup>	Anthropometric variables (n=9), cardiovascular risk factors (n=9), dietary intake	rs1049353	No association with anthropometric variables (n=9), dietary intake (n=9) or adipocytokines (n=5) Mutant allele associated with better cardiovascular profile (lower TGs, insulin and HOMA <sub>ir</sub> , higher HDL)	Neutral = 28 Positive = 1 Negative = 3

				(n=9) and adipocytokines (n=5)		No association with glucose, TC, LDL-C, CRP, lipoprotein (a).	
de Luis et al. 2011c <sup>46</sup>	94	24/70	BMI>30 kg/m <sup>2</sup>	Anthropometric variables (n=9), cardiovascular risk factors (n=9), dietary intake (n=5) and adipocytokines (n=5)	rs1049353	No difference in basal and post-treatment anthropometric measurements (n=18), cardiovascular risk factors (n=18), dietary intake (n=5) or cytokines (n=5) between the two genotypes Mutant allele associated with decreased resistin, leptin and IL-6 following weight loss	Neutral = 46 Negative = 3
de Luis et al. 2011d <sup>23</sup>	917	Not reported	BMI>30 kg/m <sup>2</sup>	Anthropometric variables (n=7), biochemical variables (n=7) and adipocytokines (n=3)	rs1049353	Mutant allele associated with lower glucose, insulin and HOMA <sub>1c</sub> values and decreased prevalence of metabolic syndrome	Negative = 4 Neutral = 28
de Luis et al. 2013 <sup>76</sup>	258	64/194	BMI>30 kg/m <sup>2</sup> subject to one of two hypocaloric diets	Anthropometric variables (n=7), cardiovascular risk factors (n=8) and adipocytokines (n=5)	rs1049353	No difference between basal and post-treatment anthropometric measurements (n=14), cardiovascular risk factors (n=16) or adipocytokines (n=8) Mutant allele associated with lack of decrease in leptin following both diets.	Neutral = 38 Positive = 2
de Luis et al. 2014 <sup>8</sup>	86	44/42	BMI>30 kg/m <sup>2</sup> with T2DM, given liraglutide	Anthropometric variables (n=8), cardiovascular risk factors (n=8)	rs1049353	BMI, weight, fat mass and WC higher in wild-type group pre- and post-treatment. No difference in biochemical parameters (n=8) pre-treatment No difference in decrease in BMI, weight, fat mass, fat free mass, WC, WHR, SBP, DBP, glucose, HDL-C, TGs or insulin between wild- or mutant-type group following treatment Wild-type allele associated with better improvements in LDL-C and TC Mutant allele associated with better improvements in HOMA <sub>1c</sub> levels following treatment.	Neutral = 17 Positive = 2 Negative = 5
de Luis et al. 2015a <sup>71</sup>	190	57/133	European	BMI, weight, fat mass, WC, WHR, SBP, DBP Glucose. TC. LDL-C, HDL-C, TGs, insulin, HOMA <sub>1c</sub> , CRP. Adiponectin, resistin, leptin. Measured at baseline, 3 months and 9 months following diet.	rs1049353	No association with any measured parameters.	Neutral = 54
de Luis et al. 2015b <sup>30</sup>	341	120/221	BMI>30 kg/m <sup>2</sup>	Anthropometric variables (n=8), cardiovascular risk factors (n=8) and dietary intake (n=9)	rs1049353	No associations with anthropometric variables (n=8) Mutant-type group associated with lower TGs and higher HDL-C No associations with glucose, TC, LDL-C, insulin, HOMA <sub>1c</sub> , CRP or dietary intake measurements (n=9)	Neutral = 24 Positive = 1 Negative = 1

de Luis et al. 2015c <sup>31</sup>	896	0/896	Female, BMI>30 kg/m <sup>2</sup>	Anthropometric variables (n=7), cardiovascular risk factors (n=7)	rs1049353	No association with BMI, weight, fat mass, WC, WHR, SBP, DBP, glucose, LDL-C, TC, insulin or HOMA <sub>1c</sub> . No association with energy, carbohydrate, fat, monounsaturated fat, polyunsaturated fat, protein or fibre intake. Mutant-type group associated with lower TGs and higher HDL-C, and lower cholesterol and saturated fat intake.	Neutral = 19 Positive = 1 Negative = 3
Dinu et al. 2011 <sup>75</sup>	305	-	Romanian, 35-75 years	Adiponectin	rs1049353	Mutant allele associated with higher adiponectin levels	Positive = 1
Gazzerro et al. 2007 <sup>11</sup>	419	237/182	Italian, >65 years	BMI	rs1049353	Mutant allele associated with lower BMI	Negative = 1
Hu et al. 2010 <sup>9</sup>	518	209/173	Chinese Han	BMI, WC, SBP, DBP, HOMA <sub>1c</sub> , TGs, TC, HDL-C, LDL-C	rs1049353	Mutant allele associated with lower BMI, WC, HOMA <sub>1c</sub> , TG levels and prevalence of MetS. No association with SBP, DBP, TC, HDL-C or LDL-C	Neutral = 5 Positive = 1 Negative = 4
Muller et al. 2007 <sup>35</sup>	2,595	768/1827	BMI>30 kg/m <sup>2</sup>	BMI	rs1049353 rs1535255 rs2023239 rs6454676 rs754387 rs806370 rs806379 rs9353527	No association with obesity for any polymorphism studied	Neutral = 8
Peeters et al. 2007 <sup>14</sup>	1,064	455/568	BMI>30 kg/m <sup>2</sup>	WC, WHR, fat mass (kg), fat mass (%)	rs1049353	Homozygosity for mutant allele associated with increased WHR and WC in obese men only. No other associations	Neutral = 6 Positive = 2
Aberle et al. 2007 <sup>85</sup>	451	264/187	BMI>30 kg/m <sup>2</sup>	BMI, TGs, cholesterol, LDL-C, HDL-C, VLDL-C, lipoprotein (a), glucose	rs1049353 rs324420	No associations with rs1049353 Mutant allele associated with greater decrease in TGs and total cholesterol following low fat diet	Neutral = 14 Negative = 2
Frost et al. 2010 <sup>13</sup>	783	783/0	Danish, 20-29 years, male	Body weight parameters (n=3) MRI measurements (n=4), biochemical markers (n=7)	rs1049353  rs10485179 rs806381	Wild-type allele associated with visceral and intermuscular fat mass, higher TGs. No associations with total body fat mass, BMI, WHR, abdominal and femoral subcutaneous fat mass or any biochemical markers (n=7) No association with rs10485179 or rs806381 for any endpoint (n=28)	Neutral = 41 Positive = 3
Jaeger et al. 2008 <sup>47</sup>	756	309/447	Caucasian	Anthropometric (weight, height, BMI, WHR, WC), biochemical (HDL-C, LDL-C, TGs, glucose) and lifestyle factors (n=3)	rs1049353 rs12720071 rs806368	No associations No associations rs806368 associated with increased WHR. No other associations.	Neutral = 35 Positive = 1
Reinhard et al. 2008 <sup>97</sup>	1,968	1,072/896	MI patients	Obesity, arterial hypertension, hypercholesterolaemia, T2DM.	rs4649119 rs3003328 rs1130321 rs2229586 rs2229579	rs3003328 and rs2229586 associated with hypercholesterolaemia. No other associations with any SNP and endpoint.	Neutral = 50 Positive = 2

					rs4649124 rs2501431 rs16828926 rs2501390 rs2501399 rs9424339 rs7530595 rs17338135		
Baye et al. 2008 <sup>49</sup>	1,560	Not reported	Obese and non-obese subjects	Anthropometric parameters (BMI, WC, hip circumference, WHR), insulin responsiveness (insulin, glucose, HOMA <sub>ir</sub> ), lipids (TC, LDL-C, HDL-C, TGs)	rs1049353 rs12730071 rs806366 rs806368 rs806369 rs806370	rs806366 associated with BMI and TGs rs806370 associated with HDL-C rs806369 associated with TGs, TC rs806368 associated with TGs No associations with obesity parameters, insulin responsiveness or lipid levels for rs1049353 or rs12720071 Haplotype H4 associated with higher BMI, insulin and lipids.	Neutral = 56 Positive = 9
Lenarcik-Kabza et al. 2014 <sup>82</sup>	130	0/130	Subjects with PCOS	Anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMA <sub>ir</sub> )	rs1049353 rs10485170 rs2023239 rs6454674 rs806381 rs806368	Homozygosity for rs2023239 wild-type allele associated with higher TC and LDL-cholesterol in women with PCOS. No other associations. No association with anthropometric or biochemical measurements for any other polymorphism in study.	Neutral = 64 Positive = 2
Milewicz et al. 2010 <sup>43</sup>	348	0/348	Postmenopausal women	Anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index)	rs1049353 rs10485170 rs12720071 rs2023239 rs6454674 rs806368 rs806381	rs1049353 associated with higher android fat deposit and percentage of android fat. No other associations. No associations for any other polymorphism.	Neutral = 89 Positive = 2
Bordicchia et al. 2010 <sup>88</sup>	280	Not reported	Obese hypertensive	BMI, WC, TC, HDL-C, LDL-C, TGs, glucose, SBP, DBP, MBP, MetS	rs12720071	Mutant allele associated with lower prevalence of metabolic syndrome. No other associations observed.	Neutral = 10 Negative = 1
Dinu et al. 2010 <sup>73</sup>	191	Not reported	Romanian, 35-75 years	Glucose	rs12720071	No association with impaired glucose metabolism	Neutral = 1
Russo et al. 2007 <sup>3</sup>	1,213	1,213/0	White adult male	BMI, WC, subscapular skinfold thickness	rs12720071  rs806368	Mutant allele associated with increased WC and subscapular skinfold thickness.  No association.	Neutral = 4 Positive = 2

Schleinitz et al. 2010 <sup>83</sup>	2,774	Not reported	Two German cohorts	BMI, WHR, fat, glucose, insulin, leptin, adiponectin	rs1049353 rs12720071 rs806368 rs806369 rs806370	No associations observed.	Neutral = 35
Wangensteen et al. 2010 <sup>22</sup>	5,011	1,235/3,776	Norwegian Caucasian	BMI	<b>CB1:</b> rs1049353 rs12720071 rs806368 <b>NAPE-PLD:</b> rs13232194 rs17605251 rs11487077 rs12540583 rs6465903	Haplotype I (combination of alleles of rs13232194, rs17605251, rs11487077, rs12540583 and 6465903) protective against severe obesity	-
Benzinou et al. 2008 <sup>36</sup>	1,932	Not reported	Caucasian		rs2023239 rs806381	Mutant alleles of both polymorphisms associated with higher BMI	Positive = 2
Zhuang et al. 2012 <sup>94</sup>	2,812	0/2,812	Chinese female, 50-64 years	Anthropometric measurements (BMI, WC, WHR, SBP, DBP) and biochemical (TC, TGs)	rs2023239 rs806381	No association between rs2023239 and any anthropometric or biochemical measurements rs806381 mutant allele associated with increased TGs. No association with this allele and any anthropometric measurements.	Neutral = 13 Positive = 1
Laczmanski et al. 2011 <sup>91</sup>	348	0/348	Polish post-menopausal women	Anthropometric measurements (Weight, BMI, WC, fat (%), android fat deposit, gynoid fat deposit, SBP, DBP) and biochemical measurements (TC, HDL-C, LDL-C, TGs, glucose, insulin, FIRI).	rs10485170 rs2023239 rs6454674 rs806381	No associations with any polymorphism.	Neutral = 60
de Luis et al. 2010b <sup>44</sup>	279	0/279	Obese female	Anthropometric variables (n=9), cardiovascular (n=9) and dietary intake (n=9)	rs324420	No association with anthropometric measurements or dietary intake. Mutant allele associated with lower TGs, glucose, HOMA <sub>ir</sub> and IL-6 levels	Neutral = 23 Negative = 4
de Luis et al. 2010c <sup>28</sup>	143	0/143	Obese female	Anthropometric variables (n=9), metabolic variables (n=9), dietary intake (n=9)	rs324420	No association with anthropometric measurements. Mutant allele associated with lower glucose, insulin, HOMA <sub>ir</sub> and visfatin levels. No association with dietary intake.	Neutral = 23 Negative = 4
de Luis et al. 2010d <sup>52</sup>	67	16/51	BMI >40 kg/m <sup>2</sup> , bariatric surgery patients	Anthropometric variables (n=6), metabolic variables (n=5)	rs324420	No differences between genotypes in baseline anthropometric measurements. Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.	Neutral = 32 Negative = 12

						No association with metabolic variables at baseline, 3 months, 9 months or 12 months.	
de Luis et al. 2011e <sup>27</sup>	122	33/89	BMI >30 kg/m <sup>2</sup>	Anthropometric variables (n=9), cardiovascular (n=9) and dietary intake (n=5)	rs324420	Lower insulin, HOMA <sub>1c</sub> and CRP in mutant-type group at baseline. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, TC, LDL-C, HOMA <sub>1c</sub> , CRP and TGs. No association with dietary intake measurements at baseline or 3 months.	Neutral = 35 Negative = 11
de Luis et al. 2012 <sup>50</sup>	799	248/551	BMI >30 kg/m <sup>2</sup>	Anthropometric variables (n=7), metabolic variables (n=7) and adipocytokines (n=5)	rs324420	Mutant allele associated with higher insulin and HOMA <sub>1c</sub> in patients without MetS. No differences in anthropometric, metabolic parameters or adipocytokines between genotypes in MetS or non-MetS subjects.	Neutral = 36 Positive = 2
de Luis D et al. 2017 <sup>26</sup>	1,027	280/747	BMI >30 kg/m <sup>2</sup>	Anthropometric variables (n=5), cardiovascular (n=10) and dietary intake (n=9)	rs3123554	Mutant-type group had higher BMI, weight, fat mass, WC TGs, insulin and HOMA <sub>1c</sub> than wild-type group. No difference in dietary intake between genotypes.	Neutral = 17 Positive = 7
Ketterer et al. 2014 <sup>21</sup>	2,006		Subjects at risk of T2DM	BMI, weight, WHR, total body fat (%)	rs3123554 rs2229579 rs2501392 rs9424398 rs4625225	rs3123554 mutant allele associated with lower BMI, weight and body fat in women. Carriers also lost less weight following lifestyle interventions No associations found with any other polymorphism.	Neutral = 17 Negative = 3
Jensen et al. 2007 <sup>72</sup>	5,738	2,887/2,851	Obesity	BMI, WC, WHR Glucose, insulin, C-peptide, HOMA <sub>1c</sub> , TGs, TC	rs324420	No association with any measured parameters.	Neutral = 9
Martins et al. 2015 <sup>42</sup>	200	100/100	Normal/obese	Anthropometric measurements (n=6), metabolic variables (n=7), adipocytokines/endocannabinoids (n=7)	rs324420	Mutant allele associated with lower adiponectin levels and higher AEA levels. No other associations observed.	Neutral = 18 Negative = 2
Monteleone et al. 2008 <sup>19</sup>	189	0/189	Subjects with binge-eating disorder	Obesity, binge-eating disorder	rs324420	Mutant-allele associated with overweight and obesity, but not binge-eating disorder	Neutral = 1 Positive = 2
Muller et al. 2010 <sup>51</sup>	10,498	5,072/5,426	Obese children and adolescents, siblings and parents.	Obesity (childhood, adult)	rs324419 rs324420 rs2295632 rs873978	rs324420 wild-type allele associated with childhood obesity but not adult obesity.	Neutral = 7 Positive = 1

Sipe et al. 2005 <sup>17</sup>	2,667	Not reported	Caucasian, black and Asian subjects	BMI	rs324420	Homozygosity for mutant allele associated with increased BMI.	Positive = 1
de Miguel-Yanes et al. 2011 <sup>25</sup>	2,411	1,157/1,254	Caucasian	HOMAir, insulin, glucose.	rs10485171 <b>rs806365</b> rs7766029 <b>rs806366</b> rs806368 rs12720071 rs1049353 <b>rs806369</b> rs806371 rs806374 rs806375 rs806376 rs806380 rs7752758 rs12528858 rs12205430 rs6454673 rs6914429	rs806365 wild-type allele associated with higher HOMAir, but not glucose in initial testing. Those in bold underwent meta-analysis for association with HOMAir, glucose and insulin levels, with rs806365 being associated with HOMAir and insulin levels.	Neutral = 42 Negative = 4
Mutombo et al. 2011 <sup>16</sup>	1,452	678/774	Japanese, 25-74 years	Anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA1c, T2DM)	rs806368 rs806378 rs806377 rs806376 rs806375 rs12720072 rs12195101 rs806374 rs806371 rs806370 rs806369 rs1049353 rs16880260 rs4707436 rs12720071 rs45516291 rs7738931 rs12189668 rs806366 rs7766029 rs16880218 rs806365	rs806368 mutant allele associated with increased BMI, WC, SBP and obesity. No other associations.	Neutral = 272 Positive = 4

					rs35951010		
Lieb et al. 2009 <sup>64</sup>	2,415	1,143/1,275	Caucasian	BMI, WC, visceral adipose tissue	rs10485171 rs806365 rs7766029 rs806366 rs806368 rs12720071 rs1049353 rs806369 rs806371 rs806374 rs806375 rs806376 rs806380 rs7752758 rs12528858 rs12205430 rs6454673 rs6914429 rs12073998 rs6703669 rs3766246 rs324420 rs324419 rs2295633 rs12029329 rs324425 rs7520850	No associations with BMI, waist circumference or visceral adipose tissue for any polymorphism.	Neutral = 81
Caruso et al. 2012 <sup>93</sup>	118	60/58	Elderly (65-75 years)	BMI, TC, HDL-C, TGs, glucose and dietary variable (n=14)	rs1049354	Mutant allele associated with decreased dietary cholesterol and saturated fats.	Neutral = 17 Negative = 2
Buraczynska et al. 2014 <sup>74</sup>	667	330/337	Polish, T2DM subjects	T2DM, HbA1c, BMI.	rs1049354	No association with T2DM. Mutant allele associated with increased BMI in T2DM subjects	Neutral = 1 Positive = 2
Durand et al. 2008 <sup>20</sup>	5,109	2,274/2,835	French Caucasian	Child obesity, adult obesity, T2DM, BMI, glucose, insulin, WC, HDL-C, TC, TGs.	rs324420	Wild-type genotype associated with class III adult obesity, but not child obesity or T2DM. Mutant allele associated with increased HDL-C	Neutral = 8 Positive = 1 Negative = 1
Liu et al. 2011 <sup>10</sup>	242	-			rs1049353	In patients with coronary artery disease, the mutant allele was associated with lower BMI, HOMA <sub>ir</sub> and TGs, and higher HDL-C	
Zeng et al. 2011 <sup>53</sup>	191	109/82	MetS subjects, healthy controls	BMI, WC, SBP, DBP, HOMA <sub>ir</sub> , TGs, TC, HDL-C, LDL-C	rs324420	Wild-type allele associated with lower WC, BMI, HOMA <sub>ir</sub> and TGs, and higher HDL-C levels in subjects with MetS. No association with SBP, DBP, TC or LDL-C levels.	Neutral = 4 Positive = 4 Negative = 1



Feng et al. 2013 <sup>79</sup>	1,006	497/509	European	HDL-C	rs806371	Mutant allele associated with lower HDL-C levels	Negative = 1
Tiwari et al. 2010 <sup>92</sup>	183	124/59	Schizophrenia/schizoaffective disorder	Antipsychotic-induced weight gain	rs806378 rs806380 rs2180619 rs9450902 rs10485170	rs806378 mutant allele associated with antipsychotic-induced weight gain	Neutral = 4 Positive = 1
Vazquez-Roque et al. 2011 <sup>98</sup>	62	19/43	Overweight/obese	Gastric motor function variables (n=6)	rs324420 rs806378	rs806378 mutant allele associated with increased gastric volume. No associations between rs324420 and gastric motor function.	Neutral = 11 Positive = 1
Wang et al. 2012 <sup>12</sup>	544	263/281	T2DM subjects	BMI, SBP, DBP, glucose, HOMA <sub>1c</sub> , TGs, TC, HDL-C, LDL-C, HbA <sub>1c</sub> , CRP	rs1049354	Mutant allele associated with lower BMI, SBP, HOMA <sub>1c</sub> and CRP and higher HDL-C. No other associations seen.	Neutral = 6 Negative = 4 Positive = 1
Grolmusz et al. 2013 <sup>54</sup>	130	0/130	Women with PCOS, healthy controls	BMI, WC, glucose, insulin, HOMA <sub>1c</sub>	rs324420	Mutant allele associated with lower insulin, glucose and HOMA <sub>1c</sub> values in healthy controls, but not PCOS subjects.	Neutral = 7 Negative = 3
Zhang et al. 2009 <sup>32</sup>	1,644	Not reported	Subjects of Northern European ancestry	BMI, HDL-C, TGs, insulin sensitivity	rs324420	Mutant allele associated with increased TGs and reduced levels of HDL-C	Neutral = 2 Positive = 1 Negative = 1
Suárez-Pinilla et al. 2015 <sup>69</sup>	65	44/21	Subjects with first episode psychosis	BMI at baseline and 3 years follow-up	rs1049353 rs2023239 rs1535255	No association between any polymorphism and BMI.	Neutral = 6
Bellini et al. 2015 <sup>95</sup>	240	0/240	Female, BMI >30 kg/m <sup>2</sup>	BMI, HOMA <sub>1c</sub> , TC, TGs, HDL-C	rs35761398	No association with BMI, HOMA <sub>1c</sub> , TC, HDL-C or triglyceride levels	Neutral = 5
Knoll et al. 2012 <sup>48</sup>	453	Not reported	Overweight/obese children and adults	BMI, weight, TC, LDL-C, HDL-C, TGs, glucose, insulin, HOMA <sub>1c</sub> , SBP, DBP.	rs324420	No association with any measured outcome	Neutral = 11
Papazoglou et al. 2008 <sup>96</sup>	303	153/150	Obesity, obesity and MetS	BMI	rs324420	No association with BMI	
Harismendy et al. 2010 <sup>99</sup>	289	-	BMI >40 kg/m <sup>2</sup>	BMI	rs16830415 rs9832418 rs547801 rs520154 rs60963555 rs684358 rs9852837 rs9829319 rs9829320	No association with BMI No association with BMI No association with BMI Associated with high BMI Associated with high BMI Associated with high BMI Associated with high BMI Associated with high BMI No association with BMI	Neutral = 7 Positive = 8

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rs9829321	No association with BMI
rs9877819	No association with BMI
rs28753886	No association with BMI
rs35948688	Associated with high BMI
rs874546	Associated with high BMI
rs2011138	Associated with high BMI

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