Abstract

Aim. – To assess the association of POMC haplotype-tagged single nucleotide polymorphisms (htSNPs) with the development of type 1 diabetes (T1D) in a Caucasian population.

Methods. – All exons, intron 1, and approximately 6-kb upstream and 3-kb downstream of the POMC gene were bidirectionally resequenced to identify DNA polymorphisms in 30 individuals. Allele frequencies were determined (60 chromosomes) and efficient htSNPs were selected using the htSNP2 programme. Genotyping was performed in 390 cases, 339 controls and 245 T1D parent-offspring trios, using Taqman, Sequenom and direct-sequencing technologies.

Results. – Thirteen polymorphisms (two novel) with a minor allele frequency greater than 1% were identified. Six POMC htSNPs (rs3754863 G > A, ss161151662 A > G, rs3754860 C > T, rs1009388 G > C, rs3769671 A > C, rs1042571 G > A) were identified. Allele and haplotype frequencies were similar between case and control groups (P > 0.60 by permutation test), and assessment of allele transmission distortion from informative parents to affected offspring also failed to find any association. Stratification of these analyses for age-at-onset and HLA-DR risk group (DR3/DR4) revealed no significant associations. A haplotype block of 9.86-kb from rs3754863 to rs1042571 was identified, encompassing the POMC gene. Comparison of haplotype frequencies identified the GGCGAG haplotype as protective against T1D in 12.9% of cases vs. 18.3% of controls: \( \chi^2 = 8.18, P_c = 0.03 \) by permutation test.

Conclusion. – The POMC SNP haplotype GGCGAG may have a protective effect against T1D in the UK population. However, this finding needs to be replicated, and the cellular and molecular processes influenced by this POMC haplotype determined to fully appreciate its impact.

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Keywords: Type 1 diabetes; Proopiomelanocortin; Polymorphism; Haplotype; Genetics

Résumé

Analyse dans une population britannique de l’association des haplotypes du gène de la pro-opiomélanocortine (POMC) avec le diabète de type 1.

Objectif. – Évaluer l’association des haplotypes de polymorphismes mononucléotidiques (htSNPs) du gène de la POMC avec le développement du diabète de type 1 (DT1) dans une population caucasienne britannique.

Méthodes. – Tous les exons, le premier intron et les régions s’étendant sur 6 kb en amont et 3 kb en aval ont été séquençés chez 30 sujets pour identifier les polymorphismes. Les fréquences alléliques ont été déterminées (60 chromosomes) et les htSNPs d’intérêt ont été sélectionnés à l’aide du programme htSNP2. Un génotypage a été réalisé dans 390 cas, 339 témoins et 245 trios parents-enfant DT1, en utilisant les méthodes Taqman, Sequenom et par séquençage direct.

Abbreviations: htSNP, haplotype tagged SNP; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; LOD, logarithm of odds; MAF, minor allele frequency; POMC, proopiomelanocortin; SD, standard deviation; SNP, single nucleotide polymorphism; T1D, type 1 diabetes.

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Résultats. – Treize polymorphismes (dont deux nouveaux) avec une fréquence de l’allèle mineur supérieure à 1 % ont été identifiés. Six htSNPs du gène POMC (rs3754863 G > A, ss161151662 A > G, rs3754860 C > T, rs1009388 G > C, rs3769671 A > C, rs1042571 G > A) ont été identifiés. Les fréquences alléliques et haplotypiques étaient similaires entre les cas et les témoins ($P > 0.6$ par test de permutation) et la recherche d’une distorsion de transmission allélique parents-enfants atteint n’a pas montré d’association. La stratification de ces analyses selon l’âge de début du DT1 et les groupes HLA-DR à risque (DR3/DR4) n’a révélé aucune association significative. Un bloc haplotypique de 9,86 kb (de rs3754863 à rs1042571) englobant le gène POMC a été identifié. L’haplotype GGCGAG a été identifié comme protecteur vis à vis du DT1, présent chez 12,9 % des cas vs. 18,3 % des témoins ($\chi^2 = 8,18, P = 0,03$ par test de permutation).

Conclusion. – L’haplotype GGCGAG du gène de la POMC pourrait avoir un effet protecteur vis-à-vis du DT1 dans la population britannique. Cette observation doit être confirmée et les processus cellulaires et moléculaires influencés par cet haplotype de POMC déterminés.

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Mots clés : Diabète de type 1 ; Pro-opiomélanocortine ; Polymorphisme ; Haplotype ; Génétique

1. Introduction

Type 1 diabetes (T1D), the most common autoimmune disease of childhood, is characterized by acute-onset ketoacidosis and insulin dependency due to destruction of pancreatic beta cells [1]. The incidence of T1D is currently increasing in Europe by 3.9% annually in those aged 0–14 years, with the number of new cases predicted to reach 24,400 per year by 2020 [2]. Such a rapid change cannot be entirely attributable to changes in the prevalence of susceptibility genes, but rather to an increase in environmental risk factors associated with the initiation of autoimmunity and acceleration of disease progression [3,4].

One of the factors linked to beta-cell destruction is weight gain, leading to an increase in insulin resistance and possibly to immunogens released from apoptotic beta-cells, thereby increasing the likelihood of autoimmune injury [4,5]. The prevalence of childhood obesity has risen significantly in recent years [6] and exhibits a parallel trend with the increased frequency of diabetes [7]. It has been widely reported that the age at onset of T1D is inversely related to body mass index (BMI) [8–12], with a relative weight during childhood of greater than 120% being associated with a greater than two-fold risk of T1D [13].

Paediatric obesity has a complex aetiology, central to which is control of appetite and energy expenditure [14]. The leptin signalling pathway plays a pivotal role in energy homeostasis. The adipocyte-derived hormone leptin controls feeding behaviour, augments fatty-acid oxidation in skeletal muscle and attenuates insulin secretion, while enhancing whole-body insulin sensitivity and glucose disposal [15]. Peripheral signals – in particular, from leptin, insulin and glucose – converge on a molecular level in the prohormone gene proopiomelanocortin (POMC) [16].

POMC, also known as “corticotropin-lipotropin precursor”, is located on 2p23.3, spans approximately 7.99-kb and contains three exons [17]. POMC undergoes extensive and tissue-specific post-translational processing to yield a range of biologically active peptides, depending on the types of processing enzymes expressed in the tissue. The pituitary corticotrophs produce adrenocorticotropic hormone (ACTH) and β-lipotropin. In contrast, the hypothalamus produces gamma-melanocyte-stimulating hormone (γ-MSH), α-MSH, cortocotropin-like intermediary peptide (CLIP) and β-lipotropin, which further breaks down to produce γ-lipotropin and β-endorphin (Fig. 1) [18]. α-MSH has potent protective and anti-inflammatory

![Diagram of POMC tissue-specific cleavage](image_url)

Fig. 1. Diagram of POMC tissue-specific cleavage (at the numbers indicated) to produce smaller active molecules under the action of peptidases. Adapted from Nussey and Whitehead (2001) [18].

effects. It is also implicated in nuclear factor-kappa B activation, expression of adhesion molecules and chemokine receptors, production of proinflammatory cytokines and mediators, interleukin (IL)-10 synthesis, T-cell proliferation and activity, inflammatory cell migration, expression of antioxidative enzymes and apoptosis [19].

Evidence from both human and murine genetic studies has established that POMC-derived peptides synthesized in neurons of the hypothalamus play a central role in the control of energy homeostasis [20]. POMC gene expression is decreased in streptozotocin (STZ)-induced insulin-dependent diabetic rats while insulin administration increases POMC gene expression in normal animals [21]. Screening for POMC in subjects with juvenile-onset obesity has identified a number of mutations and polymorphisms within the gene [22,23]. These include an Rsf1 C1798T polymorphism in the promoter (rs3754863), G1032C in intron 1 (rs1009388), a 9-bp insertion deletion in exon 3 (rs10654394) and G8246A in the 3′ UTR (rs1042571).

Our hypothesis was that disruption of MSH processing as a result of SNPs within the POMC gene may alter T1D risk. To investigate the role of common POMC polymorphisms in T1D, all exons, intron 1, intron-exon boundaries, and 6-kb upstream and 3-kb downstream of the POMC gene were screened by dideoxy sequencing to identify all polymorphisms, and to allow the construction of common haplotypes. Introns 2 and 3 were excluded, as it is unlikely that they contain polymorphisms of functional significance. Haplotype-tagged single nucleotide polymorphisms (htSNPs) were investigated, using a combination of case–control and family-based association analyses.

2. Research design and methods

2.1. Subjects

Ethical approval was obtained from the Queen’s University of Belfast Research Ethics Committee, and all recruited individuals gave their written informed consent to participate prior to starting the study. Diagnosis of T1D was based on increased plasma glucose levels to above the diagnostic threshold values defined for T1D and an absolute dependency on insulin. Probands were derived from a Northern Ireland register of patients with T1D who had been diagnosed before their 15th birthday [24].

For the case-control study, 390 probands were recruited; both parents and grandparents of each proband were born in Northern Ireland. DNA from both parents was also available for 245 of the 390 probands. These trios were used for the family-based association study. Controls (n = 339) were derived from the Young Hearts 2000 Study collection, a group of children selected from a random sample of Northern Ireland schools [25].

2.2. SNP discovery

Gene regions of interest were divided into overlapping fragments (average 500-bp length and minimum 50-bp overlap) and amplified by polymerase chain reaction (PCR), using HotStar Taq DNA polymerase (Qiagen, Crawley, UK). Polymorphisms were identified in 30 of the Young Hearts 2000 Study participants [25] by DNA sequencing. Genotype information from observed SNPs provided data for haplotype construction and identification of htSNPs. All sequencing was performed on an ABI 3100 Genetic Analyzer (Applied Biosystems, Warrington, UK), using BigDye® terminator v3.1 cycle-sequencing kits (Applied Biosystems) according to the manufacturer’s instructions.

2.3. Genotyping

POMC fragments of 400 bp, 250 bp and 280 bp incorporating the SNPs rs3754863, ss161151662 and rs1009388, respectively, were amplified by PCR, using HotStar Taq DNA polymerase (Qiagen), and genotyped by sequencing on an ABI 3730 Genetic Analyzer (Applied Biosystems), using BigDye® terminator v3.1 cycle-sequencing kits (Applied Biosystems) according to the manufacturer’s instructions. All subjects were genotyped for rs1042571, using Taqman®-nuclease assay (C_8722914_10) on an ABI Prism 7900HT Sequence Detection System (Applied Biosystems). Genotyping for POMC rs3754860 and rs3769671 was performed, using the Sequenom® MassARRAY iPLEX™ (Sequenom, Hamburg, Germany) technology according to the manufacturer’s instructions.

Stringent quality-control measures were applied to all assays, and included placing cases and controls on the same plate, non-template controls, sample duplicates, and DNA of known genotype and of the father–mother–proband trios used to assess quality by checking for Mendelian errors. Genotypes were scored independently by two trained personnel, and confirmed in a subset of samples (n = 48) for rs3754860, rs3769671 and rs1042571 variants by sequencing on an ABI 3730 Genetic Analyzer.

2.4. Statistical analysis

The extent of linkage disequilibrium (LD) between pairs of SNPs was quantified by Lewontin’s D’ value [26]. Using the genotyping data from the 30 Young Hearts’ control samples, where SNPs had a minor allele frequency [MAF] greater or equal to 5%, haplotypes across the genetic region encompassing POMC were inferred using SNPHAP software [27]. The htSNPs were then identified using the htSNP2 package, with the r² threshold set at greater or equal to 0.8 [28].

Genotype frequencies were assessed for Hardy-Weinberg equilibrium (HWE) using a χ² goodness-of-fit test with the level of significance set at P < 0.01. The χ² test for contingency tables was used to compare genotype and allele frequencies between case and control subjects with the level of significance set at P < 0.05. Subgroup analyses were also performed using cases stratified by gender, age at diagnosis of diabetes (<5 years and ≥5 years) and HLA-DR risk group [DR3/DR4 heterozygotes (n = 94), other carriers of DR3 (n = 72), other carriers of DR4 (n = 69) and any non-DR3 or -DR4 individuals (n = 9)]. Assessment of allele transmission distortion from the expected 50:50 transmission from informative parents to offspring was performed, using the transmission disequilibrium test (TDT). Haplotype analyses for both case-control and family data were performed using Haploviz [29]. Both single-marker and multi-
marker haplotypes were assessed simultaneously for association with T1D using the Haplovie permutation test \((n = 10,000\) repetitions), which provided \(P\)-values that were corrected for multiple testing. The sample sizes employed in the case-control study were sufficient to result in 90% power to detect as significant \((P < 0.05)\) an odds ratio (OR) of 1.7 for a directly genotyped SNP with an MAF of at least 10% in the control population, and greater than 80% power for a tagged SNP with the same characteristics.

### 3. Results

#### 3.1. Subjects

Of the 390 cases analyzed, 207 (53.1%) were male and 138 (35.4%) had been diagnosed with T1D before age 5 years. The 339 controls had an average age at recruitment of 13.4 years, and 164 (48.4%) were male.

#### 3.2. htSNP identification

All three exons, exon-intron boundaries, intron 1, and approximately 6-kb upstream and 3-kb downstream of the \(POMC\) gene were screened for genetic polymorphisms by DNA sequencing. In total, approximately 11-kb of DNA sequences were screened for each of the 30 individuals. A total of 13 polymorphisms (12 SNPs, one indel), two of which were novel (ss161151662, rs1009388) (\(D^2 = 0.73\)) and greater than 80% power for a tagged SNP with the same characteristics.

#### 3.3. Polymorphism analysis

The distribution of genotypes was in HWE for all variants identified during screening, and in htSNPs in both case and control groups. No significant differences were detected in genotype frequencies for the individual htSNPs in cases compared with controls \((P = 0.01)\), it did not withstand correction \((P = 0.09; \text{Table 1})\). In contrast, analysis of haplotype distribution revealed a lower frequency of the GGGGAG haplotype in patients than in controls, and remained significant even after applying the Haplovie permutation test \((12.9\% \text{ cases, } 18.3\% \text{ controls}; \text{Table 2})\).

TDT analysis was performed for \(POMC\) rs3754863, ss161151662, rs3754860, rs1009388, rs3769671 and rs1042571 polymorphisms on 245 trios (cases from case–control study

### Table 1

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
<th>(P)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3754863</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>739 (94.7)</td>
<td>647 (96.0)</td>
<td>0.26</td>
<td>0.75 (0.44–1.27)</td>
</tr>
<tr>
<td>A</td>
<td>41 (5.3)</td>
<td>27 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>350 (89.7)</td>
<td>310 (92.0)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>39 (10.0)</td>
<td>27 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ss161151662</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>659 (84.5)</td>
<td>536 (79.3)</td>
<td>0.01</td>
<td>1.42 (1.08–1.88)</td>
</tr>
<tr>
<td>G</td>
<td>121 (15.5)</td>
<td>140 (20.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>276 (70.8)</td>
<td>211 (62.4)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>107 (27.4)</td>
<td>114 (33.8)</td>
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<td></td>
</tr>
<tr>
<td>rs3754860</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>513 (65.8)</td>
<td>456 (67.3)</td>
<td>0.55</td>
<td>0.94 (0.75–1.17)</td>
</tr>
<tr>
<td>T</td>
<td>267 (34.2)</td>
<td>222 (32.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>178 (45.6)</td>
<td>147 (43.4)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>157 (40.3)</td>
<td>162 (47.8)</td>
<td></td>
<td></td>
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<tr>
<td>TT</td>
<td>55 (14.1)</td>
<td>30 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1009388</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>552 (70.8)</td>
<td>490 (72.3)</td>
<td>0.53</td>
<td>0.93 (0.73–1.17)</td>
</tr>
<tr>
<td>C</td>
<td>228 (29.2)</td>
<td>188 (27.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3769671</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>757 (97.1)</td>
<td>657 (97.5)</td>
<td>0.62</td>
<td>0.85 (0.43–1.67)</td>
</tr>
<tr>
<td>C</td>
<td>23 (2.9)</td>
<td>17 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>367 (94.1)</td>
<td>321 (95.2)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>23 (5.9)</td>
<td>15 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>0 (-)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1042571</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>648 (83.1)</td>
<td>550 (81.1)</td>
<td>0.33</td>
<td>1.14 (0.87–1.51)</td>
</tr>
<tr>
<td>A</td>
<td>132 (16.9)</td>
<td>128 (18.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>269 (69.0)</td>
<td>225 (66.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>110 (28.2)</td>
<td>100 (29.5)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>11 (2.8)</td>
<td>14 (4.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* As expected genotype counts are small, two rare genotypes were combined.

and parents where available). No significant distortions in allele transmissions were observed for the \(POMC\) polymorphisms in informative families \((\text{Table 3})\). Transmissions of \(POMC\) haplotypes from heterozygous parents to diabetic offspring all failed to reach statistical significance \((\text{Table 4})\). Furthermore, stratification by age at the time of diabetes diagnosis (<5 years and ≥5 years), gender and for case HLA-DR risk group (DR3/DR4

### Table 2

<table>
<thead>
<tr>
<th>Haplotype(^a)</th>
<th>Case frequency (%)</th>
<th>Control frequency (%)</th>
<th>(\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATGAG</td>
<td>33.7</td>
<td>32.3</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>GACCAA</td>
<td>15.3</td>
<td>16.4</td>
<td>0.35</td>
<td>0.55</td>
</tr>
<tr>
<td>GCCGAG</td>
<td>12.9</td>
<td>18.3</td>
<td>8.18</td>
<td>0.004</td>
</tr>
<tr>
<td>GAGCAG</td>
<td>13.9</td>
<td>12.2</td>
<td>0.92</td>
<td>0.34</td>
</tr>
<tr>
<td>GACCGG</td>
<td>13.6</td>
<td>11.3</td>
<td>1.75</td>
<td>0.19</td>
</tr>
</tbody>
</table>

\(^a\) Defined on rs3754863, ss161151662, rs3754860, rs1009388, rs3769671 and rs1042571 markers.

Overall \(\chi^2 = 9.38; df = 4; P = 0.052\).
heterozygotes, other carriers of DR3, other carriers of DR4) revealed no statistically significant differences in either case-control or TDT studies (data not shown).

4. Discussion

Genes regulating the leptin signalling pathway are particularly important for human energy homeostasis [15,16], key to which are the POMC gene products that play a central role in glucose sensing and regulation via the melanocortin system [31]. Disruption of MSH processing as a result of SNPs within the POMC gene may potentially alter T1D risk. The present study was the most extensive screening to date of the POMC gene and its surrounding area for polymorphisms, and identified htSNPs and examined common haplotypes for association with T1D.

We identified 13 polymorphisms, including two novel variants (ss161151661, ss161151662). Comparison of our resequenced data with that available in HapMap (accessed 30 November 2009) revealed that less than half of the resequenced SNPs (MAF ≥ 1%) in our study were recorded, and that all HapMap variants were located in either intron 1 or 3 of the POMC gene [32]. As previously reported, strong LD was detected between a number of POMC variants [30], with common haplotypes (>5%) being determined via six htSNPs (the 5′ sequence SNPs rs3754863 G > A, ss161151662 A > G, rs3754860 C > T, intronic SNPs rs1009388 G > C and rs3769671 A > C, and the 3′ UTR SNP rs1042571 G > A). The MAFs of the polymorphisms identified were in agreement with those reported in previous publications [22,30] and the National Center for Biotechnology Information (NCBI) database [33]. No significant genotype or allele associations were identified in this first case-control and TDT study to examine the role of common polymorphisms of the POMC gene in the development of T1D, despite stratification by age at the time of diabetes diagnosis (<5 years and ≥ 5 years), gender and case HLA-DR risk group. The G allele of ss161151662 was less frequently seen in cases compared with controls (15.5% vs. 20.7%), but failed to reach significance after correction (Pc = 0.08). A common GGCGAG haplotype, however, was identified, and was significantly protective against T1D (12.9% cases vs. 18.3% controls; Pc = 0.03). Although this haplotype did not reach significance in the TDT analysis, the results did show a trend in a similar direction (Table 4).

The only functional SNP (rs10654394) detected in our POMC screen was a 9-bp insertion between nucleotides 6979 and 6998 of exon 3, leading to the insertion of three amino acids (Ser-Ser-Gly) between codons 94 and 100 in the region of the 16-kDa carboxy-terminal fragment of γ-MSH. This polymorphism is associated with differences in fasting insulin levels in childhood obesity and, in the present study, was in LD with the htSNP rs3754863 (D′ = 1.0) [34]. No significant association, however, was detected between this SNP and T1D.

The role of this POMC haplotype in the development of T1D is unclear. POMC polymorphisms have previously been associated with circulating leptin levels and body-fat distribution [30,35]; however, these were not assessed in our present study population. α-MSH, a post-translational product of POMC, antagonizes the actions of proinflammatory cytokines and is known to modulate the action of TNF-α in macrophages in an autocrine fashion [36]. α-MSH also induces regulatory T cells and has been shown to protect against experimental autoimmune encephalomyelitis [37]. Disruption of α-MSH production may therefore, in theory, contribute to beta-cell destruction. Epigenetic regulation may also play a role in T1D risk, as the POMC promoter hypermethylation has previously been correlated with glucose levels [38,39].

The strengths of our present study include the relatively homogeneous population examined, and the use of TDT in addition to our case-control analysis, which minimized the possibility of spurious associations due to population heterogeneity. Strict genotyping quality-control measures were used with a high genotyping success rate (> 99.4%) and a 100% concordance rate between duplicate samples, including those genotyped on two different platforms. Our present study was insufficiently powered, however, to detect the rather small ORs that are now being found by genome-wide association scans (GWAS). Only one SNP (rs934778) examined in our study was included in a GWAS of T1D, giving a stratified \( P = 6.7 \times 10^{-3} \) with 1 df [40]; however, this result has not been replicated. Consequently, it is essential that our present findings be confirmed in a larger study population, and that the cellular and molecular processes influenced by this POMC haplotype be determined to fully appreciate its impact.

In conclusion, the present study has identified the POMC SNP haplotype GGCGAG, which may have protective effects against T1D in the UK population.
Conflict of interest statement

There are none to declare.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material (Table S1) associated with this article can be found at http://www.sciencedirect.com at doi:10.1016/j.diabet.2010.11.021.

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[40] Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.