Prioritization of Candidate Genes for the Effect of Fob3b1 QTL on Chromosome 15 in Mouse Models for Polygenic Obesity and Leanness using Integrative Genomics

Martin Šimon1*, Tanja Kunej1#, Nicholas M. Morton2, Simon Horvat1*

1University of Ljubljana, Biotechnical Faculty, Department of Animal Science, Domžale 1230, Slovenija, 2Nottingham Trent University, Schools of Science and Technology, Department of Biosciences, Nottingham, United Kingdom, #Authors contributed equally to the study

*Corresponding author: martin.simon@bf.uni-lj.si

Abstract: The accumulation of excess fat affects meat quality, fertility, productivity, and whole-body metabolism in farm animals. The mouse model presents an efficient tool for investigating these traits. Previous QTL analyses of the unique mouse selection lines for polygenic obesity (Fat line) and leanness (Lean line) have revealed four major obesity QTLs: Fob1, Fob2, Fob3, and Fob4. Fob3, located on chromosome 15, was later subdivided into Fob3a and Fob3b, which additionally split into Fob3b1 and Fob3b2. Of the 158 genes annotated in Fob3b1, 16 candidate genes have been previously proposed for the Fob3b1 effect. Data from whole-genome sequencing and transcriptome analyses of Fat and Lean mouse lines were integrated with obesity QTLs in cattle and pigs from Animal QTLdb and phenotypes obtained from the International Mouse Phenotyping Consortium (IMPC) and the Mouse Genome Database (MGD). Out of 158 genes located in the Fob3b1 interval we prioritized 17 candidate genes, including six previously proposed (Adgrb1, Col22a1, Cyp11b1, Dgat1, Gpihbp1 and Ly6a) and 11 novel candidates: 9030619P08Rik, Eppk1, Kcnk9, Ly6c1, Ly6d, Ly6h, Ly6i, Ly6m, Ptk2, Trappc9, and a strong candidate Ly6e that deserve further functional analyses. Biological function and literature screening for candidate genes suggest that the Fob3b1’s impact on obesity may operate through triglyceride metabolism (Dgat1 and Gpihbp1) and cytoskeletal and extracellular matrix remodelling (Ly6a, Ly6e and Eppk1). Further fine mapping, genetic and ‘omic’ studies should clarify whether the Fob3b1 effect is due to a causal genetic variant in one of the candidates or possibly due to an additive effect of a combination of these positional candidates. The applied bioinformatics approach in determining the priority of candidate genes for obesity can also serve as a model for other traits in veterinary and livestock sciences.

Introduction

Obesity, considered by many to be the epidemic of the 21st century, is broadly divided into two categories: the mono-genic type and the more common polygenic type (1,2). Obesity leads to the development of metabolic disorders such as diabetes mellitus, high blood pressure, cardiovascular diseases, and inflammation-related diseases (3). The accumulation of excess fat also affects meat quality, fertility, productivity, and whole-body metabolism in farm animals.
and is also one of the most important health and welfare issues affecting companion animals (4). Rodent models such as mice and rats serve as invaluable tools for studying the complex biology of obesity, identifying new therapeutic targets, and evaluating the efficacy and safety of potential interventions (5). There are few mouse models for the polygenic type of obesity, but they have no lean counterparts derived from the same base population. Selective breeding for desired divergent phenotypes over an extended period creates novel, polygenic, and reproducible disease models (6,7). One such mouse model was developed by divergent selection on body fat percentage over more than 60 generations, resulting in the Fat and Lean lines, which differ in fatness by a factor of five (8).

Earlier genome-wide quantitative trait locus (QTL) analyses of the two selection lines revealed four major obesity QTLs (Fob1, Fob2, Fob3, and Fob4) (9). Further experimental data showed that the QTL interval with the highest LOD (logarithm of the odds) score, Fob3 on chromosome 15, consists of two linked QTLs with smaller effects, Fob3a and Fob3b (10), which additionally split into Fob3b1, with a stronger effect, and Fob3b2 (11). Sixteen candidate genes have been proposed for the Fob3b1 effect based on previously identified obesity QTLs in mice and cattle, gene expression analyses obtained from the expression database, and based on their known biological functions (11). However, the genomic variability and differential gene expression between the Fat and Lean lines at this locus, which could significantly improve the prioritisation power for candidate genes, have not yet been fully investigated.

In the present study, integration of whole genome sequencing (WGS) focusing on single nucleotide polymorphisms (SNPs) and gene expression data of genes within Fob3b1 in white adipose tissue of the Fat and Lean lines were performed to prioritise candidate genes responsible for the Fob3b1 effect. In addition, candidates were complemented with their relatedness to obesity using gene and gene knock-out annotations and a comparative genomics approach between mouse, pigs, and cattle.

Material and methods

Whole genome sequencing (WGS) data of Fat and Lean mice were from our previous studies (12) (13). Differential gene expression data for three white adipose tissues (WAT) depots (epididymal WAT, subcutaneous WAT, mesenteric WAT) were from (14). The expression data from the three tissues were then joined and corrected for the batch effect using Empirical Bayes Analysis to obtain expression data in WAT. Gene expression was considered differential if expression differed between Fat and Lean mouse lines by at least 1.5-fold. Significance was checked at both \( p < 0.05 \) and adjusted \( p < 0.05 \) (differentially expressed genes; DEGs).

Two criteria were used for the candidate gene prioritisation for the Fob3b1 effect: 1) genes carried line-specific SNPs within coding regions (exons) according to the Ensembl Variant Effect Predictor (https://www.ensembl.org/Tools/VEP) (15) or 2.) genes were differentially expressed in WAT between the Fat and Lean mouse lines. The results were complemented with annotations related to obesity by the International Mouse Phenotyping Consortium (IMPC, www.mousephenotype.org) (16) using the search term “abnormal adipose tissue amount” and the Mouse Genome Database (MGD; http://www.informatics.jax.org) (17) using the search term “fat” in the terms for mammalian phenotypes. In addition, previous gene associations with obesity were extracted by literature screening using the Pubmed database and MeSH Terms adipog*, obes*, fat, lipid droplet and approved gene symbols and synonyms. The candidate genes were supplemented with orthologous genes within obesity-related QTLs in cattle and pigs, obtained using Animal QTLdb (https://www.animalgenome.org/cgi-bin/QTldb/, Release 50, April 25, 2023) (18), Ensembl (19), and g:Profiler (20). First, the locations of QTLs related to subcutaneous fat/adipose thickness/amount were obtained from Animal QTLdb. Second, genes within these QTLs were identified using the Ensembl Biomart. Finally, orthologous genes in mice were obtained from g:Profiler. The genomic location of Fob3b1 was obtained by converting genomic coordinates provided by (11) (71.38–76.36 Mbp, mouse NCBI36 assembly) to genome assembly GRCh38 using UCSC Genome Browser tool liftOver (https://genome.ucsc.edu/cgi-bin/hgLiftOver). Location of regulatory elements (open chromatin, enhancer, promoter, promoter flanking region, or CTCF binding site) was obtained from Ensembl database.

Results

The present study aimed to prioritize genes responsible for the Fob3b1 effect in mouse models for polygenic obesity and leanness. Two criteria were used for the candidate gene prioritisation: 1) line-specific SNPs in coding regions or 2.) differential gene expression in WAT between the Fat and Lean mouse lines. The workflow with the main results is shown in Figure 1.

The Fob3b1 interval, spanning from 15:71,550,331-76,532,745, contains 158 genes (GRCh38) of which 67 genes carry line-specific SNPs, and seven were differentially expressed in WAT between the Fat and Lean lines. By prioritization of 158 genes, we obtained 17 promising candidates: 10 genes with SNPs in coding regions (seven genes with missense variants, three genes with synonymous variants), six genes with differential expression, and Ly6e with both synonymous exonic variants in the Lean line and differential expression (Table 1). We were also interested if differential expression might be caused by potential regulatory variants (SNPs located within open chromatin, enhancer, promoter, promoter flanking region, or CTCF
binding site). Among the DEGs, two genes, both in the Lean line, carry potentially regulatory variants that may affect their expression. In 9030619P08Rik, the SNP rs31762288 is located within the open chromatin region and rs13482652 and rs32099107 are within promoter flanking region. As for Ly6e, all 42 potentially regulatory variants are within promoter flanking region. Out of 17 QTL prioritized candidates six were proposed previously (Adgrb1, Col22a1, Cyp11b1, Dgat1, Gpihbp1, and Ly6a) (11), while the 9030619P08Rik, Eppk1, Kcnk9, Ly6c1, Ly6d, Ly6e, Ly6h, Ly6i, Ly6m, PtK2, and Trappc9 are newly proposed candidate genes. Some of the 17 candidate genes have been previously associated with obesity, but genes, such as Col22a1, Eppk1, Ly6d, and Ly6m have been proposed to be associated with obesity for the first time. The comparative genomics approach revealed 14 orthologous genes located within the obesity-related QTLs in cattle, however, none of them is located within the obesity QTLs in pigs (Table 1).

**Discussion**

In the present investigation, we undertook a comprehensive analysis by integrating whole genome sequencing (WGS) and transcriptomics data from the Fat and Lean mouse lines to systematically prioritize candidate genes responsible for the observed effects of Fob3b1. Our specific emphasis was directed toward SNPs in coding regions and the gene expression profiles of genes within the Fob3b1 locus in WAT. For the SNPs in coding regions, we also included synonymous variants as accumulating experimental evidence has demonstrated that they may exert their impact on gene functions via splicing accuracy, mRNA stability, translation fidelity, protein folding, and expression (21). As many as seven out of the candidate genes in the present study are part of the LY6 (lymphocyte antigen 6 complex) family of proteins involved in a variety of functions in cell proliferation, migration, cell-cell interaction, immune cell
Table 1: 27 positional candidate genes for Fob3b1 effect; 16 from the study Prevoršek et al. (2010) (8), 17 from the present study (marked in bold), including six genes identified by both studies.

<table>
<thead>
<tr>
<th>Priority</th>
<th>Gene</th>
<th>SNPs$^1$</th>
<th>Criteria 1: Line specific SNPs in coding region</th>
<th>SNP located within regulatory region</th>
<th>Criteria 2: DEG2</th>
<th>IMPC$^3$</th>
<th>MGI$^3$</th>
<th>Cattle QTL$^4$</th>
<th>Literature associated with obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>Dgat1</td>
<td>B:17</td>
<td>B:2</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gpihbp1</td>
<td>/</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhpn1</td>
<td>B:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6a</td>
<td>L:56</td>
<td>L:3</td>
<td>L:9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyp11b1</td>
<td>L:27, F:1</td>
<td>L:1</td>
<td>✈</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyp11b2</td>
<td>L:47</td>
<td>L:2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gpr20</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adgrb1</td>
<td>L:1, F:1</td>
<td>L:1</td>
<td>L:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tsta3</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arc</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psca</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>Ly6g2</td>
<td>L:104</td>
<td>L:13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gsdmd</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naprt1</td>
<td>/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyc1</td>
<td>B:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Col22a1</td>
<td>L:388, F:499, B:283</td>
<td>L:2, F:8, B:4</td>
<td>L:17, F:21, B:12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6e</td>
<td>L:106</td>
<td>L:2</td>
<td>L:42</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trappc9</td>
<td>L:1144, F:3, B:3</td>
<td>L:8</td>
<td>L:197, B:2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9030619P08Rik</td>
<td>L:22</td>
<td>L:3</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>Ly6d</td>
<td>/</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6h</td>
<td>/</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eppk1</td>
<td>/</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kcnk9</td>
<td>L:13</td>
<td>L:1</td>
<td>L:4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6c1</td>
<td>L:49</td>
<td>L:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6i</td>
<td>L:148</td>
<td>L:3</td>
<td>L:7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ptk2</td>
<td>F:2</td>
<td>F:1</td>
<td>F:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ly6m</td>
<td>L:65, B:2</td>
<td>L:3</td>
<td>L:7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$SNPs identified in both (B), Fat (F) or Lean (L) lines; $^2$Differentially expressed gene (Fat vs. Lean); ↑ upregulated; $^3$Associated with obesity-related traits in IMPC and MGI databases; $^4$Orthologous genes in obesity-related QTL in cattle obtained from Animal QTLdb
maturation, macrophage activation, and cytokine production, mainly by regulating acetylcholine signalling (22) that has been recently linked to insulin sensitivity, low-grade inflammation, adipose dysfunction and metabolic syndrome in obesity (23,24). While four of them (Ly6a, Ly6c1, Ly6i, Ly6m) carry exonic variants in the Lean line, the remaining three (Ly6d, Ly6e, and Ly6h) were found to be expressed to a higher level in WAT of the Fat line compared to the Lean line. In addition, higher expression of an uncharacterized 9030619P08Rik, described as an LY6 pseudogene (25), and Gpihbp1, a member of the LY6 superfamily (26), was determined in the Fat line WAT. The expression of Ly6d, Ly6h, and Gpihbp1 did not depend on regulatory SNPs in our study, suggesting that there may be genetic variations in the transcriptional regulators of these three genes located elsewhere in the genome. Meanwhile, Ly6e and 9030619P08Rik in the Lean line carry potential regulatory variants that may explain their higher expression levels in the Fat line.

Among these genes, Ly6ci, Ly6a, and Ly6e are especially worth mentioning. While Ly6ci was linked to abnormal metabolic pathways in the early induction phase of autoimmune diabetes (27), altering T cell function (28), LY6A and LY6E were, in addition to their involvement in immunity (29,30) also linked to extracellular matrix remodelling (31,32). In adipose tissue of obese individuals, remodelling of the extracellular matrix, cytoskeletal reorganisation and increased cell proliferation enable the enlargement of obese adipocytes and WAT expansion (33,34). The Ly6a is not differentially expressed, however, only the Lean line carries SNPs, including two missense variants rs213983347 (V/A) and rs32279213 (D/G), located in the same exon and expressed within the protein domain Ly-6 antigen/uPA receptor-like, suggesting their effect on protein function. In cattle, LY6A has been associated with fertility, potentially by affecting growth dynamics in the unborn calf (35), and LY6D is crucial for lipid accumulation and inflammation in nonalcoholic fatty liver disease (36). Meanwhile, Eppk1, a new candidate gene with higher expression in the Fat line, is involved in cytoskeleton reorganization and cell proliferation (37). Col22a1, which encodes an extracellular matrix protein, is not differentially expressed but has several exonic variants in the Lean and Fat lines. Col22a1 has been shown to increase intramuscular fat in cattle (38) and polymorphisms in porcine COL22A1 were associated with daily weight gain (39).

Moreover, an uncharacterized 9030619P08Rik is thought to be translated into a stable circulating microprotein that may be involved in metabolic regulation and obesity (25), and Gpihbp1 regulates the lipolytic processing of triglyceride-rich lipoproteins (26). Nucleotide substitutions in GPIHBP1 cause lifelong chylomicronaemia (40). Lipolysis of triglyceride-rich particles leads to lower protective HDL cholesterol levels (41), which was previously observed in the Fat compared to the Lean line (42). Furthermore, changes in (high basal/low stimulated) lipolysis rates are associated with insulin resistance, previously demonstrated in the Fat line (43), and future weight gain in humans (44). Some polymorphisms in porcine GPIHBP1 were proposed to be genetic risk factors affecting adipose traits (45).

Among the high-priority candidates from a previous study (11) the expression of Gpihbp1 and Dgat1 was found to be higher in WAT of the Fat line, although the sequences in the two lines were identical. DGAT1 catalyses the final step of triglyceride synthesis (46), and Dgat1-deficient mice are lean and resistant to diet-induced obesity (47). In addition, DGAT1 was associated with a backfat thickness (48), fat deposition (49), and intra-muscular fat in pigs (50), and beef marbling (51). It was also identified as one of very few causative genes for milk yield and composition - fat content in cattle (52).

Other potential candidates include Cyp11b1, Adgrb1, Kcnk9, Trappc9, and Ptk2. Twenty-six of 27 line-specific SNPs were identified in the Lean line Cyp11b1, including a synonymous rs31832746. CYP11B1 is a rate-limiting enzyme in the synthesis of cortisol (53), an obesity-related steroid hormone (54) whose formation selectively increases within adipose tissue in obesity (55). Even more promising candidate for QTL effect is Adgrb1, with a potentially deleterious variant rs51566550 in the Lean line. Adgrb1−/− mice exhibited increased susceptibility to seizures, delayed growth, and reduced brain weight (56). ADGRB1 is involved in a membrane-initiated pathway to induce the expression of Abca1 (ATP-binding cassette, sub-family A (ABC1), member 1) in apoptotic cells (57) whose specific knockout in adipocytes resulted in significantly lower body weight, epidymal fat pad weight and adipocyte size due to changes in lipogenesis and lipid accretion in mice (58). Additionally, it is noteworthy that ADGRB1 may play a role in sensory food perception (59), which alone can cause metabolic changes (60,61). Similarly, Kcnk9 encodes TWIK-related acid-sensible K channel 3 (TASK3) protein that has been implicated in glucose sensing (62). Kcnk9 transcript was significantly up-regulated in mice nodose neurons fed a high-fat diet. The authors proposed it as a therapeutic target for obesity treatment (63). Adipose-specific knockout of a closely related gene Kcnk3 in mice resulted in an increased energy expenditure and resistance to obesity (64). A SNP rs2471083 near the potassium channel KCNK9 has a parent-of-origin effect on body mass index (65) and was linked to abdominal visceral fat by GWAS (66). Another candidate is Trappc9, with eight synonymous variants in Trappc9 of the Lean line. This gene plays a role in energy balance, and its deficiency leads to obesity (67). It has been linked to fat deposition-related traits in Hu sheep (68) and to body size traits in pigs (69). PTK2 (also known as focal adhesion kinase FAK), best known for its involvement in integrin signalling, was shown to influence adipocyte differentiation and to influence obesity in mice (70). In addition to its role in leptin signal transduction (71), FAK signalling controls insulin sensitivity through the regulation of adipocyte survival (72), and FAK inhibition causes insulin resistance (73). A novel missense variant 15_73264244_G/T in the Fat line may therefore
influence various signalling pathways and contribute to the obese phenotype.

However, the prioritised candidate genes may play other roles in tissues not examined in the present study. Interestingly, DGAT1, GPIHBP1, CYP11B1, ADGRB1, LY6E, and TRAPPC9 are also associated with milk production and milk composition traits in cattle and pigs, such as milk urea, lactose, protein, and fat contents and milk yield (35, 74–81) (Table 2). Importantly, recent metabolomic and proteomic investigations revealed a correlation between infant obesity and milk composition from obese or non-obese mothers (82, 83). Considering Cyp11b1, Adgrb1, Ly6e, and Trappc9, the Lean line carries exonic variants that may affect the protein function, these genes may also affect milk composition and yield and subsequently contribute to the lean or obese phenotype in our mouse models.

In summary, Fob3b1 may influence energy balance, inflammation, various signalling pathways (acetylcholine, leptin, insulin), metabolism, and cell structure in WAT, however, it may also contribute to the obese/lean phenotype by influencing milk quantity and composition. For the Fob3b1 effect on the adiposity of WAT, we propose genes involved in triglyceride metabolism (Dgat1 and Gpihbp1), cytoskeleton, and extracellular matrix remodelling (Ly6a, Ly6e, and Eppk1) as the main contributors, calling for their future functional analyses.

The control of fat deposition, energy metabolism, and immune system functioning have high economic importance in farm animals. Excess fat accumulation affects meat quality, fertility, productivity, and whole-body metabolism (84). Further functional studies of the proposed candidate genes are required to elucidate their involvement in fat deposition.

Conclusions

The present study identified 17 candidate genes potentially responsible for the Fob3b1 QTL effect in mouse models for polygenic obesity and leanness. In particular, triglyceride metabolism, cytoskeleton and extracellular matrix remodelling may be the main contributors to the effect of Fob3b1. Of the 17 most promising candidate genes, four new obesity candidates were proposed: Col22a1, Eppk1, Ly6i, and Ly6m. Further work on fine mapping and functional analyses is required to determine whether the effect of Fob3b1 is due to a causal genetic variant in one of these candidates or a combined effect of several of these positional candidates. The applied bioinformatics approach for prioritization of candidate genes for polygenic obesity in the present study can also be used to analyze other traits in veterinary medicine and livestock science. Obesity and its associated diseases pose a significant health risk, affecting not only physical well-being, but also reproductive health and overall animal welfare. These effects extend beyond farm animals to include companion animals, highlighting the interconnectedness of veterinary and human medicine in addressing obesity-related health problems in all species to improve animal health and welfare.

Table 2: Candidate orthologous genes associated with milk traits in cattle and pigs.

<table>
<thead>
<tr>
<th>Gene/Region</th>
<th>Effect on milk</th>
<th>Species/breed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADGRB1</td>
<td>urea content</td>
<td>Holstein cattle</td>
<td>Ma et al. (2023) (79)</td>
</tr>
<tr>
<td>ADGRB1</td>
<td>lactose content</td>
<td>Fleckvieh cattle</td>
<td>Costa et al. (2019) (75)</td>
</tr>
<tr>
<td>ADGRB1</td>
<td>yield</td>
<td>German Holstein cattle</td>
<td>Kaupe et al. (2007) (35)</td>
</tr>
<tr>
<td>CYP11B1</td>
<td>protein content</td>
<td>Polish landrace pigs</td>
<td>Szyndler-Nędza and Piorkowska (2015) (74)</td>
</tr>
<tr>
<td>DGAT1</td>
<td>lactose content</td>
<td>Romanian Holstein cattle</td>
<td>Tăbăran et al. (2015) (81)</td>
</tr>
<tr>
<td>GPIHBP1</td>
<td>fat content</td>
<td>cattle</td>
<td>Yang et al. (2017) (80)</td>
</tr>
<tr>
<td>LY6E</td>
<td>yield</td>
<td>Holstein cattle</td>
<td>Jiang et al. (2018) (77)</td>
</tr>
<tr>
<td>TRAPPC9</td>
<td>protein content</td>
<td>Chinese Holstein cattle</td>
<td>Khan et al. (2022) (78)</td>
</tr>
<tr>
<td></td>
<td>mastitis resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgements

This work was financially supported by the Slovenian Research and Innovation Agency (ARIS) research program P4-0220 and research project J4-2548.

Conflict of interest statement. All authors declare that they have no competing interests.

Authors’ contributions. MS: Formal analysis, writing - original draft preparation. NMIM: writing – review & editing. SH and TK: conceptualization, writing – review & editing, supervision.

Ethics approval and consent to participate. The FLI (Fat) and FHI (Lean) selection lines have been maintained in our laboratory for more than 100 generations. All mice used in this study were maintained according to local ethical and EU regulatory guidelines under the Veterinary Administration of Republic of Slovenia permit No. U34401-23/2020/6.

References

1. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet 2022; 23(2): 120–33. doi: 10.1038/s41576-021-00414-z


Določanje prioritetnih kandidatnih genov znotraj intervala Fob3b1 QTL na kromosomu 15 pri mišjih modelih za poligensko debelost in vitkost z uporabo integrativne genomike

M. Šimon, T. Kunej, N. M. Morton, S. Horvat

Izvleček: Kopičenje odvečne maščobe vpliva na kakovost mesa, plodnost, proizvodnost in presnovo pri rejnih živalih. Mišji modeli predstavljajo učinkovito orodje za raziskovanje genetske osnove teh lastnosti. Predhodne analize QTL-ov edinstvenih mišjih selekcijskih linij za poligensko debelost (debela linija) in vitkost (vitka linija) so razkrile štirje glavne QTL-e za debelost: Fob1, Fob2, Fob3 in Fob4. Fob3, ki se nahaja na kromosomu 15, je bil kasneje razdeljen na Fob3a in Fob3b, zadnji pa se dodatno razdeli na Fob3b1 in Fob3b2. Od 158 genov, anotiranih v Fob3b1, je bilo v prejšnjih študijah predlaganih 16 kandidatnih genov. Vendar pa genomska variabilnost med debelo in vitko linijo na tem lokusu ni bila v celoti raziskana. Namen te študije je bil potrditi predhodno identificirane kandidate in identificirati nove kandidatne gene, ki bi lahko bili odgovorni za učinek Fob3b1. Podatki iz celotnega genoma sekvenciranja in transkriptomskih analiz debelih in vitkih mišjih linij so bili vključeni v primerjalo analizo s QTL-i za debelost pri govedu in prašičih iz Animal QTLdb ter fenoti-pi, pridobljenimi iz Mednarodnega konzorcija za fenotipizacijo miši (IMPC) in podatkovne zbirke mišjega genoma (MGD). Izmed 158 genov, lociranih v Fob3b1, smo prednostno obravnavali 17 kandidatnih genov, vključno s šestimi predhodno predlaganimi (Adgrb1, Col22a1, Cyp11b1, Dgat1, Gpihbp1 in Ly6a) in 11 novimi kandidati: 9030619P08Rik, Eppk1, Kcnk9, Ly6c1, Ly6d, Ly6i, Ly6m, Ptk2, Trappc9 in Ly6e. Biološka funkcija in pregled literature za kandidatne gene nakazujeta, da lahko učinek Fob3b1 na debelost deluje preko metabolizma trigliceridov (Dgat1 in Gpihbp1) ter preoblikovanja citoskeleta in zunajceličnega matriksa (Ly6a, Ly6e in Eppk1). Nadaljnje natančno kartiranje, genetske in »omske« študije bodo pojasnili, ali je učinek Fob3b1 posledica vzročnega učinka ene same genetske različice ali morda aditivnega učinka kombinacije večjega števila teh pozicijskih kandidatov. Uporabljeni bioinformacijski pristop pri določanju prednostne liste kandidatnih genov za debelost lahko služi tudi kot model za preučevanje drugih lastnosti v veterinarskih in živinorejskih znanostih.

Ključne besede: povezovanje podatkov; izražanje genov; razvrstitev genov po pomembnosti; mišji modeli; debelost; QTL; posamezni nukleotid; polimorfizem