GENETIC VARIATION IN POLYADENYLATION SIGNALS OF DIFFERENTIALLY EXPRESSED mRNA ISOFORMS IN MOUSE SELECTION LINES FOR FATNESS AND LEANNESS

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Alternative polyadenylation (APA) regulates genes by creating distinct 3'-ends of transcripts by selecting different polyadenylation (PA) sites along genes, thereby influencing transcription termination and poly(A) tail addition [1]. Using the Whole-Transcriptome Termini Site Sequencing (WTTS-seq) method [2], we determined PA sites in the hypothalamus of the Fat and Lean selection mouse lines, models for polygenic obesity and healthy leanness [3]. A total of 29,091 PA sites were expressed in both lines in the hypothalamus, a major brain region regulating energy balance. They were located within 13,837 genes (86.9 %), predominantly protein-coding (93.6 %). There were 472 differentially expressed PA (DE-PA) sites in the Fat compared to the Lean line, located within 357 genes ($\log2FC \geq |1.5|$, $p_{adj} < 0.05$). Due to APA, 5,733 genes (41.4%) had multiple PA sites that could lead to mRNA isoforms. After additional filtering, we obtained 4,753 genes with more reliable PA sites producing mRNA isoforms. One hundred forty-eight of these genes had at least one DE-PA site, with 13 having multiple. Gene Ontology enrichment of 148 genes highlighted processes important for neuronal communication, including behavior, cognition, and synaptic signaling, suggesting altered brain activity in both lines. Additionally, these genes influence intracellular protein transport and organization, indicating potential changes in cellular structure and protein distribution in the Fat and Lean mice. Moreover, six genes with mRNA isoforms and DE-PA sites had SNPs within polyadenylation signals (PAS); and PAS-SNPs. Each line had three PAS-SNPs within three distinct genes: *Nrsn2* (rs27369860), *Ric3* (rs36754429), and *Rpl14* (rs263963399) genes in the Fat line; *Hlf* (rs229072835), *Taf1a* (rs32656801), and *Ints11* (rs227466545) genes in the Lean line, the latter aligning with our previous study [4]. PAS-SNPs altered the canonical AATAAA PAS motif, possibly resulting in decreased expression of these DE-PA sites, suggesting that PAS-SNPs might affect their expression. Future functional studies are needed to explore the role of PAS-SNPs and mRNA isoforms due to APA in polygenic obesity, extend the research to other metabolic tissues, and evaluate APA isoforms as novel potential therapeutic targets for obesity management.

References:

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