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Nitrogen starvation and chromatin dynamics: The role of Gcn5 in glycogen metabolism

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Abstract

Glycogen metabolism is a crucial process in *Saccharomyces cerevisiae*, enabling energy storage and adaptation to changing environmental conditions. Histone acetyltransferase Gcn5, a key component of the SAGA complex, is known to regulate gene expression through chromatin remodeling. This study investigates the role of Gcn5 in modulating glycogen metabolism under normal and nitrogen-starvation conditions. Gcn5 deletion significantly impairs yeast growth, as evidenced by slower doubling times and reduced specific growth rates, highlighting its role in metabolic adaptation. Glycogen accumulation assays revealed that *gcn5Δ* mutants accumulate more glycogen during the exponential growth phase compared to wild-type cells, suggesting that Gcn5 maintains basal glycogen levels by regulating genes involved in glycogen synthesis and degradation. However, under nitrogen starvation, *gcn5Δ* mutants exhibit drastically reduced glycogen accumulation, indicating that Gcn5 is critical for stress-responsive metabolic reprogramming. Promoter analyses of genes involved in glycogen metabolism identified overlaps between nucleosome positions and Msn2/4 transcription factor binding sites. These findings suggest that Gcn5-mediated nucleosome mobilization enables Msn2/4 binding and transcriptional activation of stress-responsive genes. The impaired glycogen storage in *gcn5Δ* mutants under nitrogen starvation underscores the essential role of Gcn5 in coordinating chromatin remodeling and transcriptional regulation during environmental stress. Overall, this study highlights the central role of Gcn5 in balancing glycogen metabolism and cellular adaptation, providing insights into its broader regulatory functions in yeast stress responses.

Keywords: Chromatin remodeling; Gcn5; Glycogen metabolism; Nitrogen starvation; *Saccharomyces cerevisiae*

1. Introduction

The budding yeast *Saccharomyces cerevisiae* serves as a powerful model organism for studying cellular responses to environmental stress. The accumulation of glycogen, along with trehalose, is a key metabolic adaptation that enhances stress resistance and survival during unfavorable conditions. This response reflects the ability of yeast cells to shift their metabolism from growth-promoting pathways to energy conservation and stress tolerance mechanisms. Glycogen is a highly branched polysaccharide of linear α (1,4)-glucosyl chains with α (1,6)-linkages, and its biosynthesis and degradation are tightly regulated by a network of enzymes and signaling pathways. Glycogen synthesis is mediated by Gsy1/2 (glycogen synthase) and Glc3 (glycogen branching enzyme), which catalyzes the addition of glucose residues to the growing glycogen chain, while Gph1 (glycogen phosphorylase) and Gdb1 (glycogen debranching enzyme) facilitates glycogen breakdown into glucose. Proper branching of glycogen is carried out by Glg1/2 (glycogen branching enzyme). These enzymes are subject to complex regulation at both transcriptional and post-translational levels, ensuring glycogen metabolism is responsive to changes in nutrient availability and cellular energy status [1, 2].

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The regulation of glycogen metabolism is closely linked to major nutrient-sensing pathways, including the Target of Rapamycin (TOR) pathway and the Protein Kinase A (PKA) pathway. The TOR pathway, a central regulator of cell growth and metabolism, promotes biosynthetic processes and suppresses stress-responsive pathways under nutrient-rich conditions. However, under nitrogen starvation or other stress conditions and rapamycin, TOR signaling is inhibited, leading to the activation of stress-adaptive responses, including glycogen accumulation and autophagy [2]. Similarly, the PKA pathway, which is activated by glucose availability, downregulates glycogen biosynthesis under high nutrient conditions but is suppressed during starvation, allowing glycogen hyperaccumulation as part of the stress response [3, 4]. The PKA pathway controls transcription of the *GSY1*, *GSY2*, *GLG1*, *GLG2*, *GPH1*, *GLC3* and *GDB1* genes which was discussed in detail by Francois and Parrou [1]. The PKA and TOR pathways controls gene expression by regulating nuclear localization of the Msn2/4p transcription factors through the anchor protein Bmh1/2p [4-6]. Under normal growth conditions, Msn2/4p remains in the cytoplasm, but under stress conditions, they are translocated to the nucleus, where they activate Msn2/4p-sensitive genes.

Chromatin remodeling complexes are central to the transcriptional activation of stress-responsive genes, allowing cells to adapt to changing environmental conditions [7-9]. *GCN5* (general control nonderepressible-5), encoding a histone acetyltransferase (HAT) and catalytic subunit of the ADA and SAGA complexes, targets specific lysine residues in the tail domains of histones H3 and H4 for acetylation [10, 11]. Acetylation of histones, particularly H3K9 and H3K14, leading to chromatin relaxation and facilitating the recruitment of transcriptional machinery to target genes. In certain instances, the role of chromatin remodeling could not be dependent on acetyltransferase activity, which operates independently of one another [8]. Gcn5 is essential for the expression of genes involved in stress adaptation, energy metabolism, and survival under adverse conditions [12].

Despite its established role in global transcriptional regulation, the specific contribution of Gcn5 to glycogen metabolism under nitrogen starvation remains underexplored. Therefore, this study investigated the role of Gcn5 in regulating glycogen metabolism in *S. cerevisiae* under both normal and nitrogen-starvation conditions, emphasizing the connection between Gcn5-mediated chromatin remodeling and gene activation through nucleosome positioning and transcription factor binding site analysis.

2. Materials and Methods

2.1. Yeast strains and growth condition

The yeast strains used in the study, *S. cerevisiae* BY4741 (MATa, *his3Δ1; leu2Δ0; met15Δ0; ura3Δ0*) and its mutant derivative Y07285 (MATa; *ura3Δ0; leu2Δ0; his3Δ1; met15Δ0; YGR252w:kanMX4*), were provided by EUROSCARF (Frankfurt, Germany). The BY4741 strain of *S. cerevisiae* contains no known mutations related to glycogen metabolism. The mutant strain comes from the BY4741 genetic background, and the *GCN5* gene has been completely removed and replaced with the geneticin resistance-codifying KanMX4 module.

2.2. Growth conditions

In order to determine the doubling times (dt) and specific growth rates (μ) of the yeast strains, yeast cells were grown in a minimal YNBD medium (0.17% yeast nitrogen base, 0.5% ammonium sulfate and 2% glucose) supplemented with auxotrophic requirements. Optical densities of yeast cultures (OD_{600}) were determined spectrophotometrically every 2 h and used for calculation of dt and μ values of yeast strains. For nitrogen starvation stress conditions, yeast strains were grown in YNBD medium till the exponential phase ($OD_{600} \approx 0.6$-0.7) at 30°C. Then yeast cultures were divided into three aliquots, and the first aliquot was harvested and used for enzyme assay. Second and third aliquots were harvested, washed, and transferred to fresh minimal medium supplemented with 0.1% proline and 0.5% ammonium sulfate, respectively. Both cultures were incubated at 30°C for 4 hour and harvested to determine glycogen contents.

2.3. Glycogen assay

The qualitative evaluation of glycogen content was conducted using the iodine-staining technique as previously outlined [13]. The quantitative glycogen content of yeasts was assessed as previously outlined [14]. Following the washing of harvested cells, they were resuspended in 250 μl of 0.25 M Na_2CO_3 and subjected to boiling for 2 hours. Subsequently, 150 μl of 1 M acetic acid and 600 μl of 0.2 M sodium acetate at pH 5.2 were added. The cell mixture was incubated at 57°C for 18 hours with 3 mU of α-amylase enzyme (Sigma, A-7420) for glycogen testing. The level of released glucose was quantified enzymatically utilizing the glucose oxidase-peroxidase system (GOD-POD assay) with a commercial kit (Fluitest®-GLU, Biocon, Germany). The glycogen content of yeasts was expressed as micrograms of glucose equivalent per milligram of wet mass (μg/mg) of the yeast cells. Results are presented as mean values from three different trials, each measured in triplicate.

2.4. Nucleosome Position Prediction Analysis

The nucleosome positioning analysis on the promoter regions of target genes (*GSY1*, *GSY2*, *GLC3*, *GDB1*, and *GPH1*) was conducted using 1000 base pair upstream sequences retrieved from the YEASTRACT database. These sequences were processed as strings in R, and the sliding window technique was employed to calculate GC content. For the sliding window approach, the window size was set to 147 base pairs, representing the typical length of DNA wrapped around a nucleosome. The GC content for each window was calculated using a custom function that counts the occurrences of guanine (G) and cytosine (C) and divides the count by the segment length. For each position in the sequence, the GC content score was calculated using the 'sapply' function. This provided a continuous GC content profile for the entire sequence. A threshold of 0.5 was applied to identify high-affinity nucleosome binding regions. Using the 'which' function, positions exceeding the threshold were recorded and further grouped based on the nucleosome window size of 147 base pairs. Median positions of these groups were identified to represent nucleosome centers.

The analyzed GC content profile and potential nucleosome binding regions were visualized using the ggplot2 library [15]. A line plot of GC content across the DNA sequence was generated, with regions exceeding the GC content threshold (50%), indicating predicted nucleosome positions, marked using red dashed lines. To further enhance visualization, heatmaps were generated to visualize binding affinity across the sequence, where high GC content regions (depicted in blue) were interpreted as areas with high nucleosome binding potential.

2.5. Transcription factor binding-position analysis

The promoter sequences of target genes (*GSY1*, *GSY2*, *GLC3*, *GDB1*, and *GPH1*) were analyzed using a 1000 bp region upstream from the transcription start site. These sequences were retrieved from the YEASTRACT database and processed as DNA strings using the DNAString function from the Biostrings R package. Msn2/ and Gcn4 transcription factor (TF) binding motifs were investigated in these promoter sequences. The Msn2/4p DNA-binding motif were obtained from the JASPAR database. The 'matchPattern' function was employed to identify exact matches of these motifs, and the start and end positions were recorded for further analysis.

We generated bar plots using the ggplot2 package to visualize the motif positions [15]. The distribution of each motif was plotted individually, and for cases with multiple motifs, combined visualizations were created to highlight overlaps and regulatory interactions. The histograms were constructed with a thousand width of 20 base pairs, and the X-axis was limited to 0–1000 base pairs with ticks at 200 base pair intervals. Distinct colors were assigned to each motif using the 'scale_fill_manual' function. Combined motif data frames were created using the 'rbind' function, allowing overlapping motifs to be displayed on the same plot.

3. Results and Discussion

3.1. Effects of Gcn5 on yeast growth

The growth rate serves as a fundamental parameter for understanding the physiological state of cells and their response to genetic or environmental factors. Therefore, the impact of specific genetic modifications or stress conditions on cellular proliferation can be assessed by quantifying how rapidly a population of cells increases in size. In this study, the growth rates of wild-type and *gcn5Δ* mutant yeast strains were determined by measuring their doubling times and calculating their specific growth rates. The results reveal a significant difference in growth dynamics between the two strains. The wild-type strain exhibited a faster doubling time of 1.677 hr and a higher specific growth rate of 0.413, indicating robust cellular proliferation under the given conditions. In contrast, the *gcn5Δ* mutant strain showed a slower doubling time of 2.029 hr and a reduced specific growth rate of 0.341, suggesting that the deletion of Gcn5 impairs the growth ability of the cells.

Growth rate analysis revealed that *gcn5Δ* yeast cells exhibited a slower growth rate compared to wild-type cells, as evidenced by a longer doubling time and reduced specific growth rate. Previous study revealing that *gcn5Δ* cells displayed moderate fermentative and more severe respiratory growth defects [16]. These results are consistent with our findings that Gcn5 is essential for proper cellular proliferation and metabolic adaptation. In the absence of Gcn5, yeast cells show impaired chromatin dynamics, which in turn activate genes necessary for optimal growth, particularly those involved in energy metabolism [12, 16]. The growth defects observed in *gcn5Δ* mutants are likely a result of impaired transcriptional regulation affecting essential metabolic pathways required for efficient cell proliferation.

3.2. Deletion of Gcn5 triggers glycogen accumulation under normal growth conditions

The amount of glycogen accumulated by cells during normal growth conditions serves as an indicator of their metabolic state and ability to store energy reserves. The glycogen accumulation levels observed in yeast cells during the logarithmic growth phase highlight a notable difference between the *gcn5Δ* mutant strain and the wild-type strain. mutant yeast cells accumulated significantly more glycogen (63.4±7.4 µg/mg cell wet weight) compared to the wild-type cells (20.2±3.2 µg/mg cell wet weight) (Figure 1).

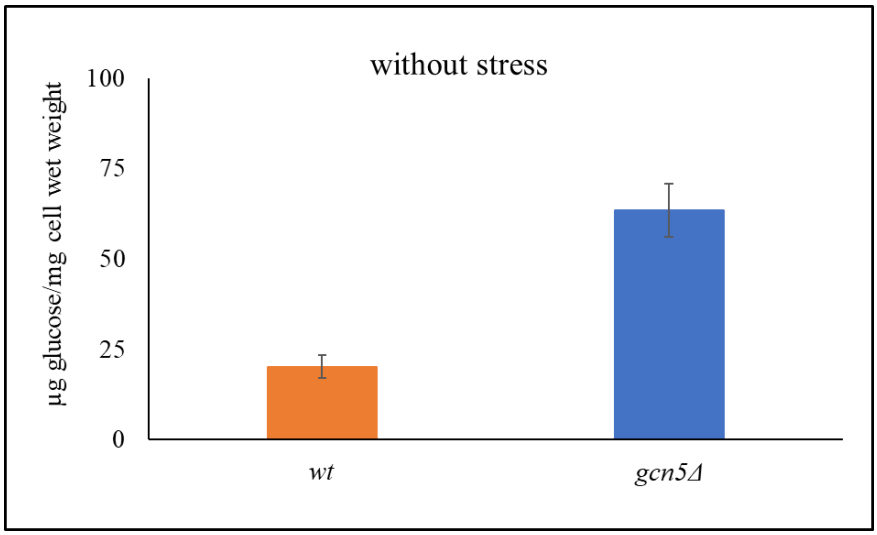

Figure 1 Glycogen accumulation of yeast cells grown exponentially

Previous studies have shown that *gcn5Δ* mutants accumulated trehalose and glycogen slightly less than wild-type yeast cells [16]. But, in our study, *gcn5Δ* mutants accumulated more glycogen than wild-type cells. Previous studies observed glycogen accumulation in *gcn5Δ* mutants during the early stationary phase, which is a period where cells typically shift from rapid growth to a more quiescent state. During this phase, cells undergo metabolic reprogramming to adapt to nutrient scarcity, and the regulation of glycogen metabolism may differ from that in the exponential phase. In contrast, our study focused on the exponential phase, where cells are actively growing and dividing. Our data suggests that Gcn5 plays a role in maintaining basal glycogen levels in yeast cells at normal growth conditions. In addition, Gcn5 may regulate the transcription of genes involved in both glycogen synthesis and degradation, and its absence may lead to the activation of genes promoting glycogen synthesis or the repression of those involved in glycogen breakdown. This would result in the increased glycogen accumulation observed in the *gcn5Δ* mutant cells.

3.3. Deletion of Gcn5 impaired glycogen accumulation during nitrogen starvation

The glycogen content in yeast was qualitatively assessed, and the result was given in Figure 2. Under nitrogen starvation, yeast colonies developed a dark orange color, reflecting significant glycogen accumulation. In the *gcn5Δ* mutant yeast, the yeast colonies displayed a very faint yellowish coloration, suggesting substantially reduced glycogen accumulation compared to the wild-type strain. Glycogen accumulation in yeast cells was also evaluated quantitatively, and the result was presented in Figure 3. Under nitrogen deprivation stress, the amounts of glycogen in wild-type cells were found to be 498.7±35.8 µg/mg, and in *gcn5Δ* mutant cells, they were 83.0±10.3 µg/mg. The glycogen accumulation in wild-type yeast cells under starvation increased 25-fold higher than that of normal growth conditions. However, in mutant cells, glycogen level remained relatively unchanged, even if a slight increase was detected, which is nonsignificant.

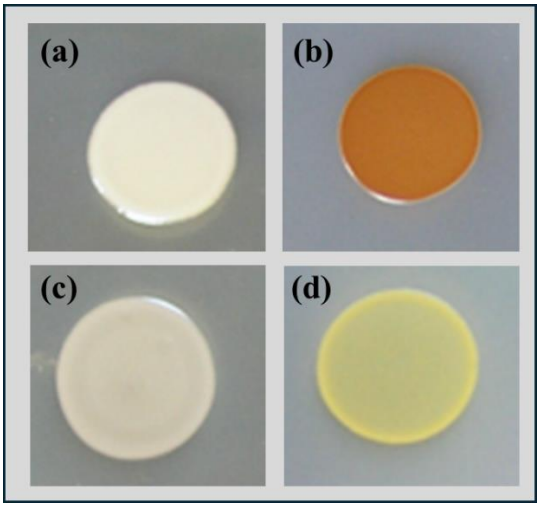

Figure 2 Iodine staining of yeast cells. (a) and (c) represent the wt and *gcn5Δ* mutant yeast cells at normal growth conditions; (b) and (d) represent the wt and *gcn5Δ* mutant yeast cells at nitrogen starvation conditions

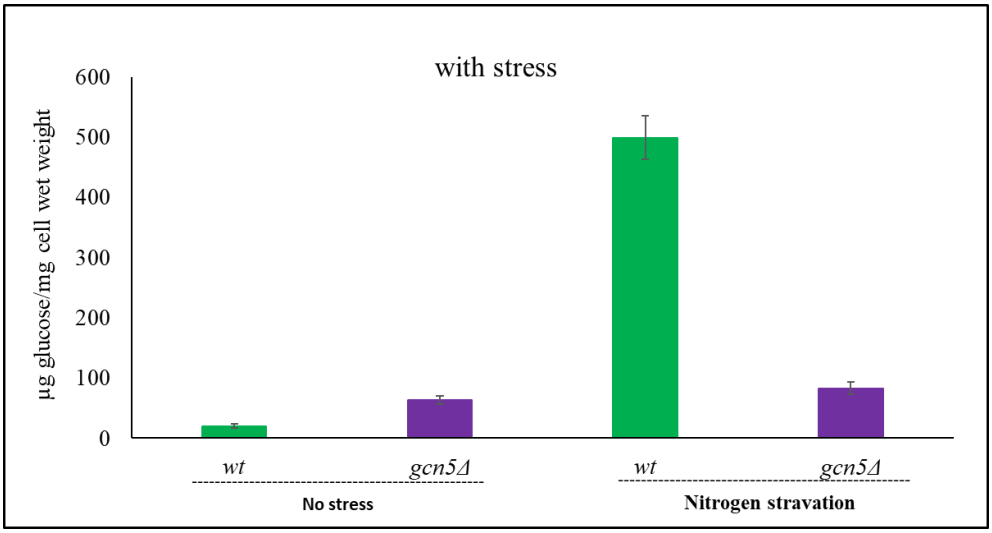

Figure 3 Glycogen accumulation of yeast cells under nitrogen starvation stress

Previously indicated that Gcn5 is necessary for redox homeostasis and protecting *S. cerevisiae* from oxidative and heat shock stress during the early stationary phase [16]. In addition, Gcn5 is specifically required for adaptation to salt stress in *S. pombe* [17]. Nitrogen starvation triggered the accumulation of storage carbohydrates, trehalose and glycogen [1, 18, 19]. The H3K9 lysine in histone H3 is known to be a target of Gcn5 in the SAGA complex [20, 21]. The acetylation level of H3K9 was dramatically reduced in mutant cells during the exponential phase compared to wild type [16]. In our results, the impaired glycogen accumulation during nitrogen starvation in the absence of Gcn5 highlights its essential role in mediating stress-responsive processes. In addition, this attenuated response may be due to the lack of Gcn5-mediated acetylation of genes involved in glycogen synthesis, which is essential for the activation of stress-responsive genes and metabolic reprogramming during nutrient deprivation. These results indicated that Gcn5 appears to play a crucial role in modulating glycogen metabolism, ensuring balanced glycogen storage under normal conditions and facilitating appropriate glycogen accumulation in response to nitrogen starvation.

3.4. Promoter Analysis

Stress responses like nutrient starvation or environmental stress tightly control genes involved in glycogen metabolism. Msn2/4 are general stress-responsive transcription factors that induce the expression of genes related to stress adaptation, including those regulating glycogen metabolism. Therefore, the promoters of genes involved in the synthesis (*GSY1*, *GSY2* and *GLC3*) and breakdown (*GPH1* and *GDB1*) of glycogen were examined to figure out the positions of

putative nucleosomes and whether these nucleosomes coincide with transcription factor binding sites. The Msn2/4 binding sites and nucleosome binding affinity and positioning within the promoter region of these genes (up to -1000 bp) were conducted using computational and visualization-based approaches.

The line plot of nucleosome positioning illustrates the periodicity of nucleosome occupancy, reflecting the ~147 bp spacing characteristic of chromatin organization, while the heatmap highlights specific regions of high nucleosome binding affinity, particularly in GC-rich sequences that enhance histone-DNA interactions. Therefore, we presented both data, as the line plot illustrates the overall distribution and periodicity, while the heatmap elucidates precise sequence-specific binding preferences. The results obtained from the line plot and heatmap analysis of genes (*GSY1, GSY2,GLC3, GPH1* and *GDB1*) revealed that the potential binding positions identified by both methods were complementary and consistent with each other. The computational analysis of nucleosome positioning within the *GSY1* promoter region revealed two possible nucleosome positions located between -825 and -975 nt and between -300 and -550 nt (Figure 4). The *GSY2* promoter exhibited a single nucleosome positioning between -300 and -550 nt (Figure 5). Likewise, the *GLC3* promoter exhibited a single nucleosome located between -225 and -375 nt (Figure 6). The *GPH1* promoter displayed a nucleosome located between -500 and -650 nt (Figure 7). The *GDB1* promoter exhibited a nucleosome between -825 and -975 nt (Figure 8).

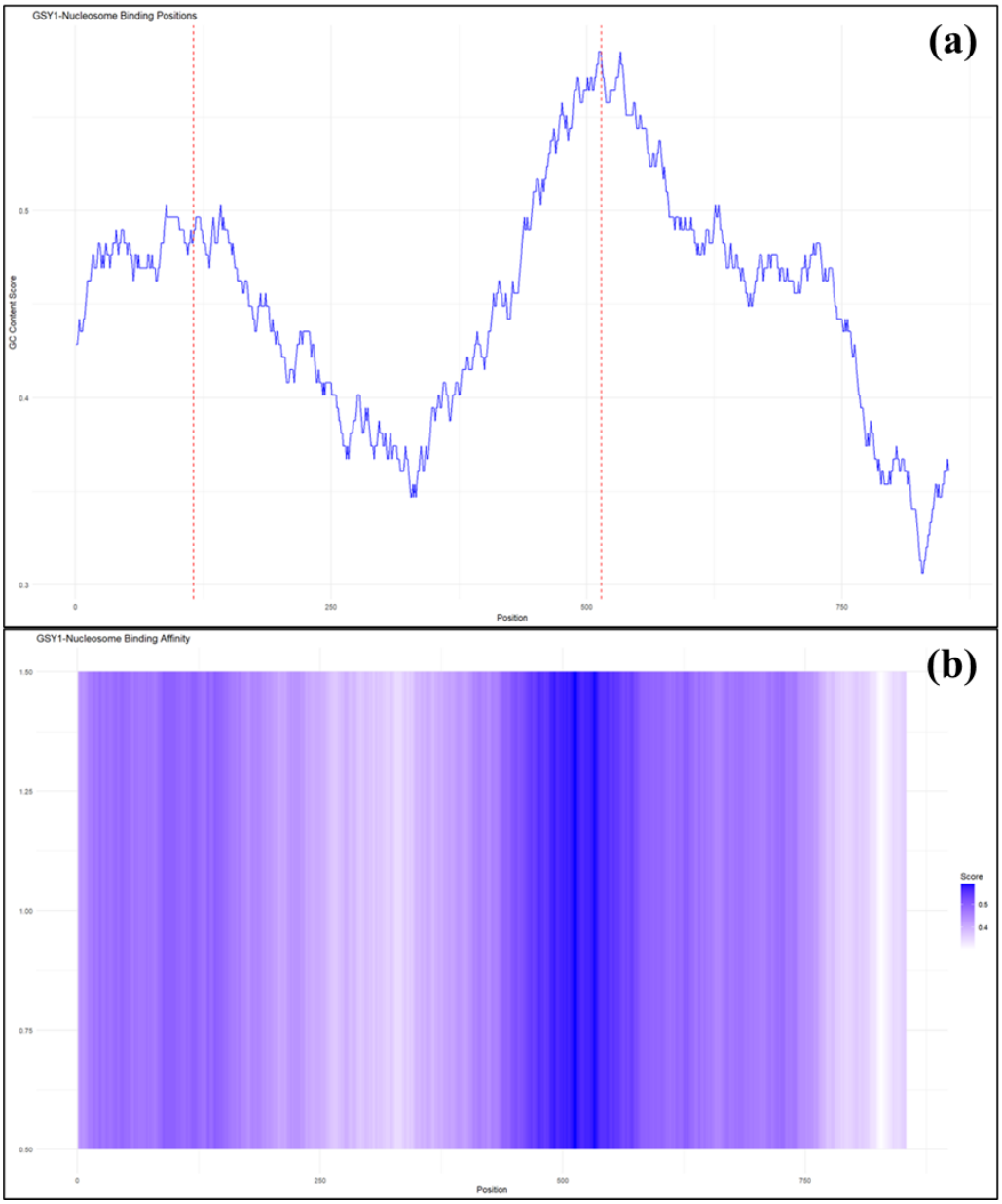

Figure 4 The line plot of nucleosome positioning (a) and the heatmap (b) analysis of *GSY1* promoter (from -1000 to -1 nt)

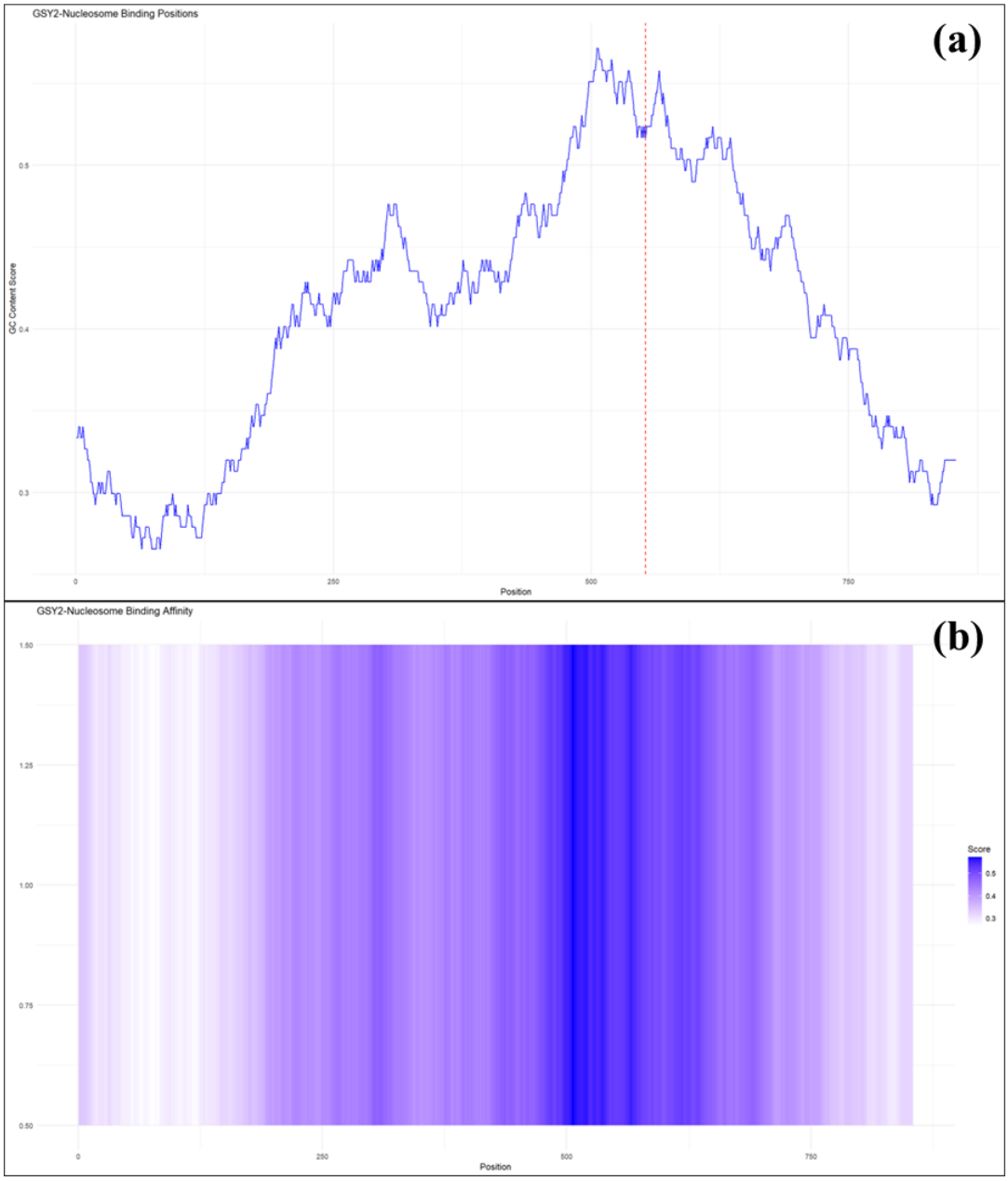

Figure 5 The line plot of nucleosome positioning (a) and the heatmap (b) analysis of *GSY2* promoter (from -1000 to -1 nt)

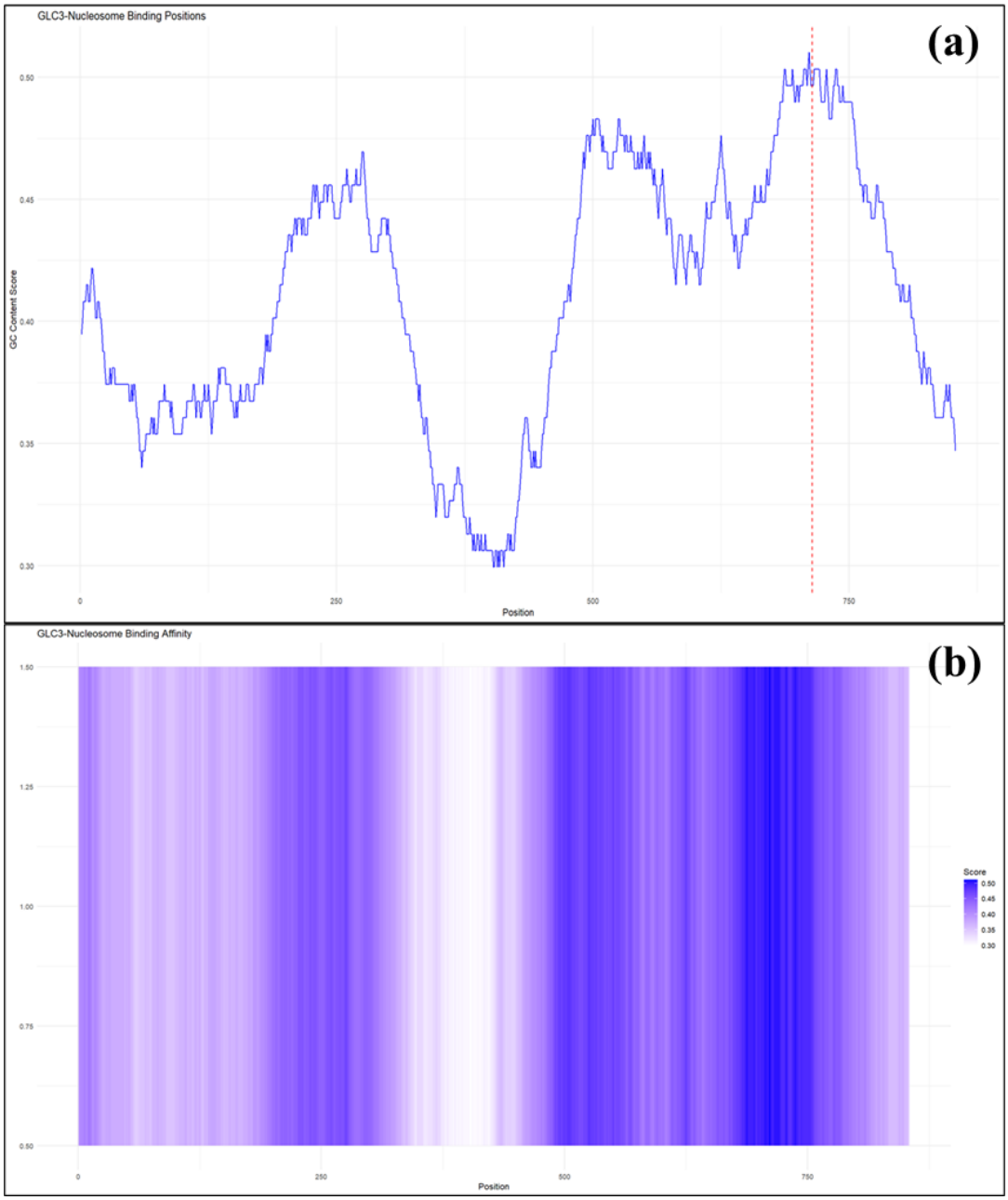

Figure 6 The line plot of nucleosome positioning (a) and the heatmap (b) analysis of *GLC3* promoter (from -1000 to -1 nt)

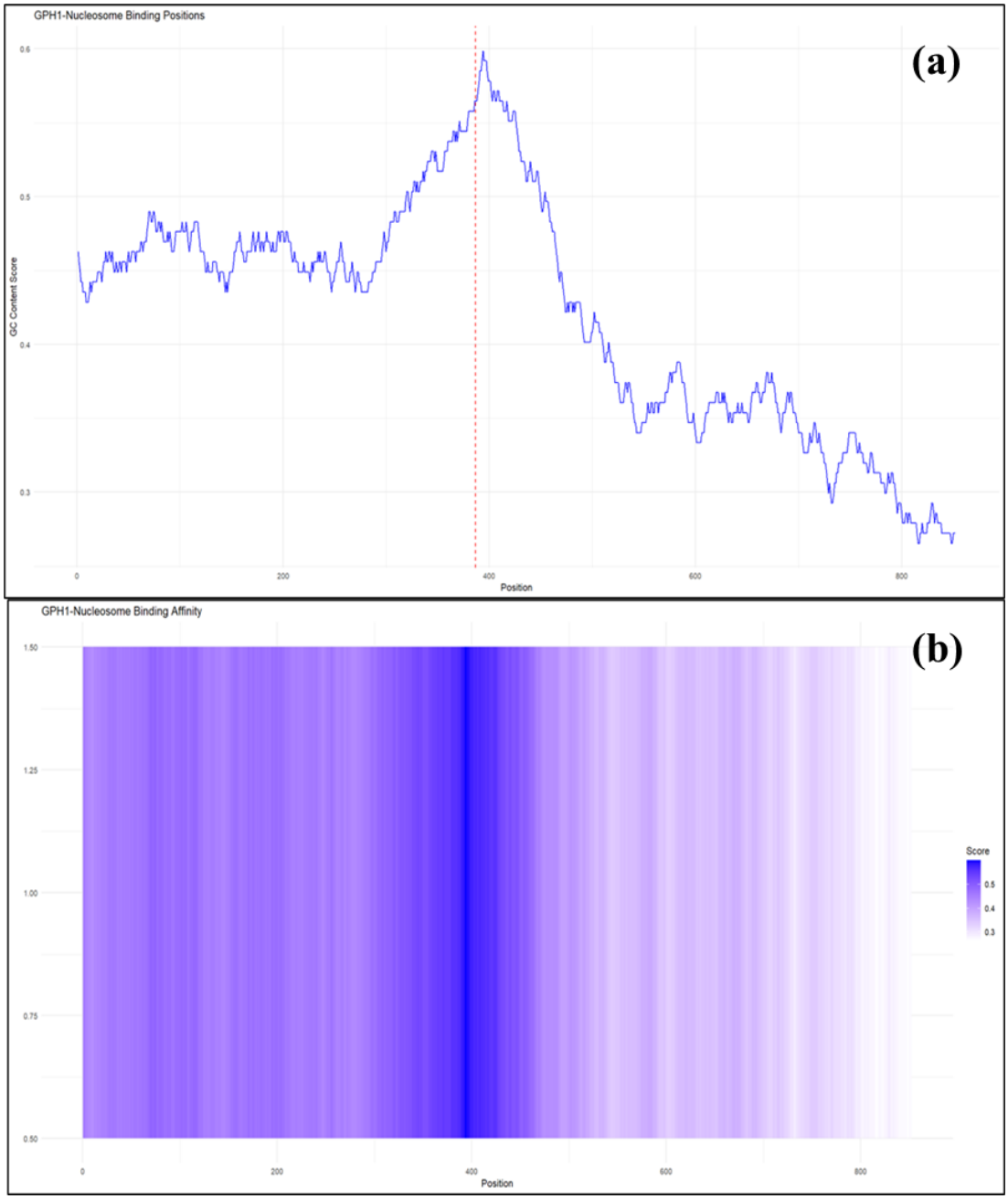

Figure 7 The line plot of nucleosome positioning (a) and the heatmap (b) analysis of *GPH1* promoter (from -1000 to -1 nt)

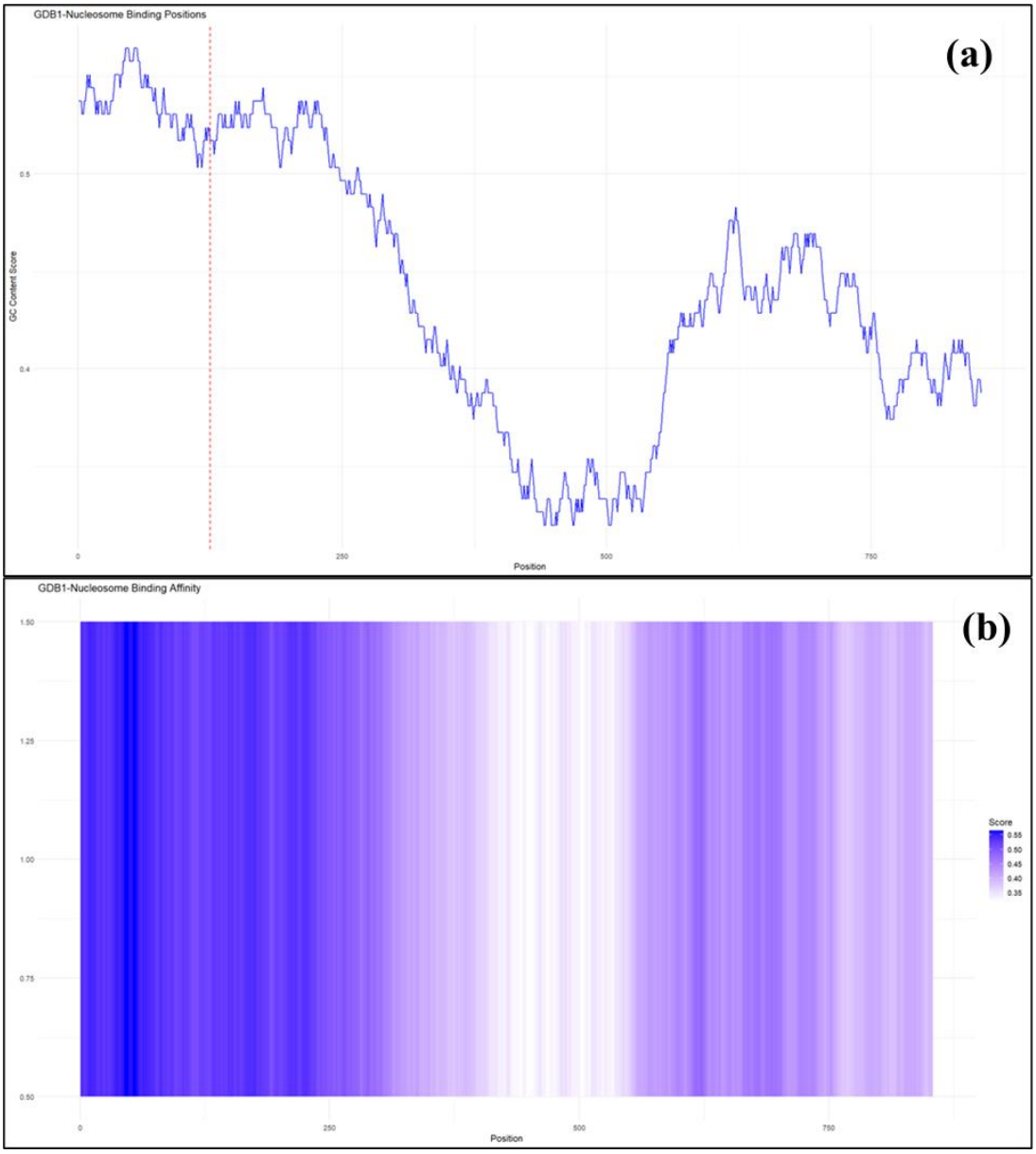

Figure 8 The line plot of nucleosome positioning (a) and the heatmap (b) analysis of *GDB1* promoter (from -1000 to -1 nt)

The computational analysis of Msn2/4 binding sites, particularly STRE motifs, identified several sites within the promoter regions of genes involved in glycogen synthesis and breakdown. The *GSY1* promoter contained two STRE sequences positioned at -332 nt and -487 nt upstream of the transcription start point. The *GSY2* promoter included two (-198 nt and -377 nt) and the *GLC3* promoter had three (-213 nt, -282 nt, and -374 nt) STRE sites in their promoters (Figure 9). The *GPH1* promoter contained three (-326 nt, -357 nt, and -545 nt), while the *GDB1* promoter possessed only one STRE site at -192 nt upstream of the transcription start site (Figure 10).

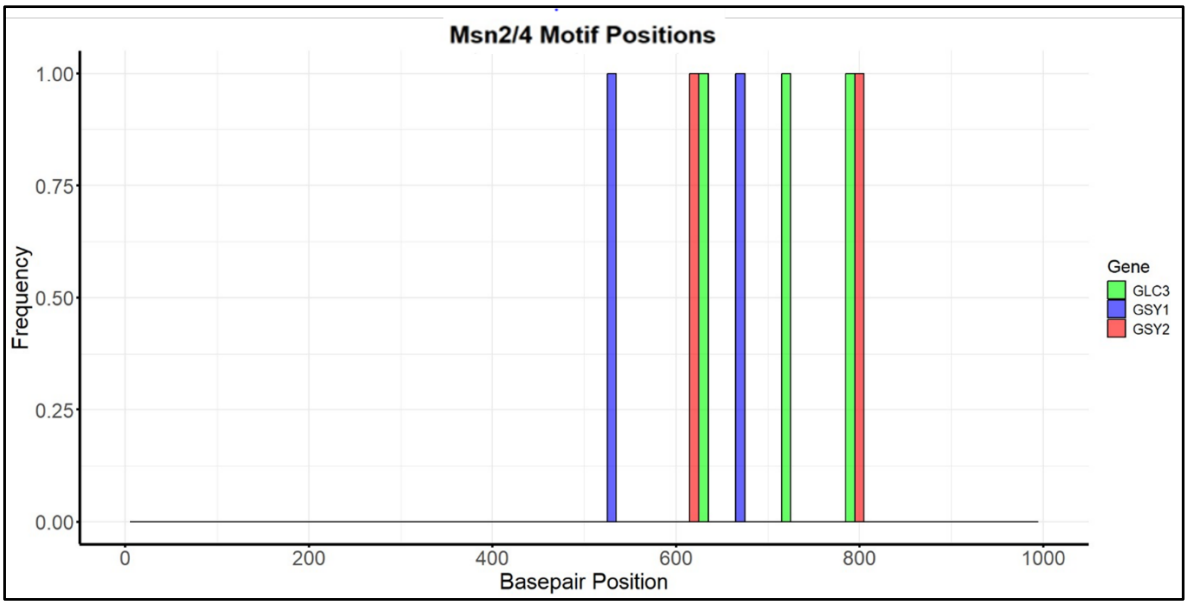

Figure 9 Msn2/4 binding sites within the promoter regions of genes involved in glycogen synthesis. 1000 corresponding to -1 in the graph and the positions of STRE sequences discussed in text

Based on these results, at least one of the Msn2/4 binding sites in the *GSY1* (-487), *GLC3* (-282), and *GPH1* (-545) promoters overlapped with nucleosome, suggesting that histone modifications (e.g., acetylation) might be required to loosen chromatin structure and enable Msn2/4 binding. If nucleosome mobilization does not occur, these STRE sites may remain inaccessible to Msn2/4, preventing the activation of transcription. This would likely lead to impaired expression of these glycogen metabolism genes, disrupting the adaptive responses required for glycogen synthesis or breakdown under stress conditions.

Figure 10 Msn2/4 binding sites within the promoter regions of genes involved in glycogen breakdown. 1000 corresponding to -1 in the graph and the positions of STRE sequences discussed in text

Msn2 and Msn4 are zinc finger DNA-binding proteins that specifically bind to the stress response element (STRE) 5′-AGGGG (or 5′-GGGGA) sequences during stress [22, 23]. Msn2/Msn4 affects the expression of genes that are up-regulated at stress conditions such as heat stress, osmotic stress, and carbon starvation stress [23-25]. It has been previously determined that *msn2/msn4* mutant yeast cells accumulate fewer glucose stores after heat shock because of a lower basal *TPS1* and *GSY2* expression [26, 27]. In addition, *GSY2* expression is induced by growth to stationary phase, heat shock or nitrogen starvation [28]. Therefore, the binding of Msn2/4 transcription factors is important for the regulation of reserve carbohydrate metabolism during stress. The overlap of nucleosome positions with these STRE

motifs suggests that histone modifications, particularly acetylation, play a crucial role in making these binding sites accessible to Msn2/4. Previously reported that the activation of *HSP12* occurs through Gcn5's chromatin remodeling ability rather than its HAT (histone acetyltransferase) activity, indicating that Gcn5p plays a critical role in chromatin remodeling during gene activation in response to stress, such as H_2O_2 treatment, without significantly influencing histone acetylation at the HSP12 locus [8]. Therefore, we can speculate that Gcn5 may enhance the transcription of genes particularly involved in glycogen synthesis by mobilizing histones at the promoter through its chromatin remodeling activity, and so the glycogen accumulation was hindered in Gcn5 mutant yeast cells.

The findings from this study suggest that Gcn5 plays a central role in regulating glycogen metabolism in yeast, both under normal growth conditions and during stress. By facilitating nucleosome mobilization and enabling the binding of transcription factors like Msn2/4, Gcn5 ensures proper gene expression and metabolic adaptation. The impaired glycogen accumulation in *gcn5Δ* mutants under nitrogen starvation further emphasizes the importance of Gcn5 in responding to environmental stressors. These results suggest that Gcn5-mediated histone acetylation is a critical mechanism for regulating glycogen metabolism in response to changing nutrient availability. In future studies, it would be valuable to further investigate the mechanistic role of Gcn5 in regulating glycogen metabolism and stress adaptation. Specifically, chromatin immunoprecipitation (ChIP) assays targeting H3K9 acetylation at the promoters of glycogen metabolism genes could provide direct evidence of the involvement of Gcn5 in transcriptional regulation. Additionally, exploring the effects of the Gcn5 deletion on other stress responses, such as oxidative stress or heat shock, would help clarify its broader role in cellular stress adaptation.

4. Conclusion

The critical role of Gcn5 in regulating yeast growth, glycogen metabolism, and stress adaptation was analyzed in this study. The deletion of GCN5 resulted in slower growth rates, impaired glycogen accumulation under nitrogen starvation, and altered glycogen storage under normal growth conditions. These findings underscore the importance of Gcn5 in maintaining proper chromatin dynamics, which facilitate the transcription of genes essential for cellular proliferation and metabolic adaptation. Our analysis revealed that Gcn5-mediated histone acetylation likely enhances nucleosome mobilization, enabling the binding of stress-responsive transcription factors such as Msn2/4 to their target promoters. This mechanism is crucial for the activation of glycogen metabolism genes under stress conditions, ensuring appropriate metabolic reprogramming and adaptation. The observed defects in glycogen accumulation in gcn5Δ mutants emphasize the significance of Gcn5 in balancing energy storage during normal and stress conditions. Future studies should focus on elucidating the mechanistic role of Gcn5 in chromatin remodeling and transcriptional regulation through advanced techniques such as chromatin immunoprecipitation (ChIP) assays. Additionally, exploring the broader impact of Gcn5 deletion on other stress responses, such as oxidative stress and heat shock, could provide a more comprehensive understanding of its role in cellular stress adaptation. These insights could further our understanding of chromatin regulation in cellular metabolism and stress responses, with potential implications for broader biological and biotechnological applications.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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