The global increase in obesity, particularly in Kuwait, highlights an urgent need to define the genetic and environmental determinants of fat metabolism. While using the mammalian model was advantageous, it presented drawbacks, including limited experimental manipulations and genetic complexity. Yeast offers a more accessible model due to its genetic amenability, conserved metabolism, ease of experimental manipulation, and the availability of mutant collections featuring lipid metabolic defects. However, previous reliance on viable loss-of-function collections overlooked the roles of essential genes or those masked by redundancies, thus hindering the observation of mutant phenotypes.

The proposed study aims to investigate the genetic and environmental determinants of fat storage in yeast by performing high-throughput functional genomic screens using two genetically modified collections: decreased abundance and overexpression collections. Through this, we anticipate overcoming the limitations of lethality and functional redundancy to reveal the roles of essential and redundant genes. Phenotypic anomalies will be assessed using multilayer fluorometric and chromatographic screening assays. Dynamic regulatory network models will be constructed once all necessary genetic elements have been identified. These models will quantitatively capture the transcriptional responses of yeast in different nutritional contexts using qPCR to generate predictive models of lipid accumulation based on genotype and diet.

Anticipated outcomes include 1) understanding the genetic architecture underlying lipid metabolism, 2) mapping the regulatory dynamics of lipid metabolism, and 3) identifying gene-environment interactions that modulate fat storage. This approach, which combines molecular and modeling methodologies, will elucidate biological causes for more evidence-based therapeutic development while demonstrating the predictive capacity of system-level understanding even in the absence of direct measures. Compacting obesity using targeted interventions guided by a comprehensive understanding of its underlying factors has significant potential. The duration of this project is 36 months, with a budget of KD 249,817. We anticipate that KFAS will contribute 35,000 KD in total.