CALIFORNIA STATE SCIENCE FAIR
2016 PROJECT SUMMARY

Name(s)

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Project Number

S0503

Project Title

Combating the Obesity Epidemic: Gene Knockdown and Drug Repurposing to Discover Therapeutic Targets and Novel Treatments

Abstract

Objectives/Goals

Over the past two decades, obesity rates have doubled, rising to epidemic levels in the US. Despite obesity's genetic aspects, the medical community continues to emphasize weight loss through lifestyle changes. The genetic mechanisms of obesity remain understudied, and treatments are ineffective. Thus, we developed a novel interdisciplinary approach integrating computational genomic analyses, wet lab experimentation, and virtual drug screening to shed light on the genetic causes of obesity and search for effective treatments.

Methods/Materials

First, we exhaustively assessed a massive dataset of 2.5 million mutations across 25,670 human genes and 249,796 individuals from the GIANT Consortium's genome-wide association study. We leveraged natural selection analyses to rank the functional significance of the top 80 potential obesity driver genes. Then, to study the gene candidates in the context of weight regulation and validate them for biological significance, we conducted RNA interference (RNAi) in Caenorhabditis elegans. We obtained dsRNA-expressing Escherichia coli strains that target our five most promising obesity genes. After inducing gene knockdown, we quantified the nematodes' lipid droplets and found that four out of the five knockout groups had reduced fat content. With the four genes as our drug targets, we searched for drug candidates. We created 3D structural models of the proteins of the genes and virtually screened 1,007,142 drug-like compounds from DrugBank and ZINC to search for potential obesity drugs and for FDA-approved drugs that can be repurposed.

Results

We discovered that 28 out of our 80 potential obesity driver genes have previous links to fat regulation. Four out of our top five gene candidates, upon knockdown in C. elegans, decreased lipid content by 20-70%. Our docking studies also pinpointed 40 top-binding drugs, of which 20 treat conditions associated with obesity (such as heart failure and type 2 diabetes), providing validation for our approach. The top four drug hits are FDA-approved and can be potentially repurposed into obesity treatments.

Conclusions/Discussion

Through extensive computational analyses, rigorous wet lab validation experiments, and docking studies, we identified 80 obesity gene candidates, four drug targets, and promising treatments, some of which are existing FDA-approved drugs.

Summary Statement

We developed a novel end-to-end drug discovery pipeline that starts with publicly available genomics datasets and returns a promising set of drug targets and leads, generating valuable insight into obesity genetics in the process.

Help Received

Prof. Stuart Kim of Stanford allowed us to use his lab for wet lab experimentation, and Biff Mann, a graduate student in the lab, helped us design the gene knockdown experiment. Prof. Susan Strome of UCSC provided us with the RNAi E. coli.