

# Comprehensive Analysis of Potential Genes in Brain Metastasis of Breast Cancer

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## Research

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# Abstract

**Background** Patients with brain metastasis of breast cancer have low quality of life, are prone to bad emotions such as anxiety and depression, and have poor prognosis. It is particularly important to find therapeutic targets for this type of patients.

**Methods** The differential genes between breast cancer patients with brain metastasis and simple breast cancer were screened by GSE125989 of GEO database, and the hub gene affecting the prognosis of breast cancer patients were identified by bc-GenExMiner database, and then the hub gene were analyzed comprehensively by STRING database and DAVIA database.

**Results** We found that OPA1 is a potential indicator for predicting the prognosis of Asian patients with breast cancer with brain metastasis. OPA1 is involved in affecting the composition and function of mitochondria, affecting energy supply, and is also related to the FOXO signal pathway.

**Conclusions** The effect of OPA1 on mitochondrial energy supply and its participation in FOXO signaling pathway may lead to brain metastasis of cancer. OPA1 is a potential therapeutic target for the treatment of brain metastasis of breast cancer, and further research is needed.

## Introduction

Brain metastases are metastases formed by the entry of tumor cells from other parts of the body into the brain. The primary site of brain metastasis of breast cancer is the breast. Breast cancer is the most common malignant tumor in women, with about 1 million new cases each year.<sup>[1]</sup> Related studies have found that patients with HR(-), HER-2(+) and triple-negative breast cancer are most likely to have brain metastasis.<sup>[2]</sup> In an autopsy study, 15%-35% of breast cancer patients were found to have brain metastasis, but some of them did not show signs of neurological disorders.<sup>[3-5]</sup> Breast cancer ranks second among solid cancers with metastasis to the central nervous system, and 10% - 16% of breast cancer patients with brain metastasis show brain clinical manifestations.<sup>[6]</sup> Patients with brain metastasis will show nervous system dysfunction, such as cognitive impairment, sensory impairment, headache, dizziness, nausea, vomiting and so on, which seriously affect the quality of life and life span of patients. Treatments include whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), neurosurgery, targeted therapy and chemotherapy. Radiotherapy and surgery are the main treatment, in which WBRT is the standard treatment.<sup>[7]</sup> Some studies have shown that chemotherapy and targeted therapy after WBRT can improve the prognosis of patients with brain metastasis of breast cancer.<sup>[8]</sup> In breast cancer patients with brain metastasis, patients with HER2(+) can survive for more than 2 years, which makes them more vulnerable to central nervous system damage, so, better treatment is needed.<sup>[9]</sup> The main purpose of this study is to find the potential treatment targeting indicators of breast cancer patients with brain metastasis in order to provide better treatment options for this type of patients.

## Materials And Methods

## Data source

Get the dataset that conforms to the analysis from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>). 2325 homo sapiens studies on breast cancer in the GEO database, and after careful examination, we selected the data set GSE125989(Platforms GPL571 [HG-U133A\_2] Affymetrix Human Genome U133A 2.0 Array). All the data were obtained from the online database, and no human or animal experiments were carried out in this study.

## Differential genes screening

Using the GEO2R online analysis tool in the GEO website to analyze the difference of gene expression in the dataset GSE125989. The datasets were divided into two groups: primary breast cancers and brain metastases. The volcanic map of differential genes was drawn by Origin software.

## Identification of hub genes

bc-GenExMiner (<http://bcgenex.centregauducheau.fr>), is a database dedicated to the prognosis of breast cancer, containing 21 public data sets.<sup>[10]</sup>The differential genes were map into the database for survival analysis of patients with breast cancer. The differential gene related to distant metastasis-free survival (DMFS) and overall survival (OS) of breast cancer patients were selected as hub gene.  $P < 0.05$  as statistically significant.

## PPI network construction

The Search Tool for the Retrieval of Interacting Genes (STRING) database (<http://string-db.org/>) is designed to analyze the protein-protein interaction (PPI) information. The database contains 9.6 million proteins, a total of 13.8 million protein interactions. In our study, we analyze the hub gene to get its PPI network, and finally use Cytoscape software ([www.cytoscape.org/](http://www.cytoscape.org/)) to visualize the PPI network.

## GO and KEGG pathway analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) (<https://david.ncifcrf.gov/>), a comprehensive online tool for gene function analysis, can help us understand the biological significance behind a lot of genes. Gene functions can be classified into cellular component (CC), biological process (BP), and molecular function (MF). In our study, Gene Ontology (GO) annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of the DAVID dataset were used to analyze the genes related to hub gene.  $P < 0.05$  and count  $\geq 5$  was considered statistically significant.

## Results

### Differential genes

In our study, we selected the gene expression dataset GSE125989, which contains Sixteen paired matched samples from primary breast cancers and brain metastases. All the samples came from Japan. These 16 samples are paired samples with breast cancer first and brain metastasis after a period of time. A total of 21154 differential genes were obtained by GEO2R online analysis tool, and their distribution was shown in Fig. 1. Based on  $P < 0.05$  and  $|\log_2FC| \geq 2$ , a total of 63 differential genes were screened, of which 3 were up-regulated and 60 were down-regulated.

## Hub gene

Using bc-GenExMiner database, all the differential genes were analyzed, and the gene related to DMFS and OS of breast cancer patients was selected as hub gene. We found that OPA1 was associated with DMFS and OS of breast cancer ( $P < 0.0025$ ,  $P < 0.0312$ ) (Fig. 2). The overexpression of OPA1 in patients (ER all; PR all) more likely to have distant metastasis, and the overexpression in patients(ER ; PR all)more likely to have worse outcome.

## PPI network

Using the STRING database to analyze the human protein-protein interaction (PPI) network of the OPA1, a total of 100 genes interact with the OPA1, including CDK8 and mediator complex subunit (Fig. 3).

## GO and KEGG pathway

The DAVIA database is used to analyze 100 genes related to OPA1 to obtain GO and KEGG information (Table 1).  $P < 0.05$  and count  $\geq 5$  as significant. We found that cellular component : (GO:0005741 mitochondrial outer membrane; GO:0005743 mitochondrial inner membrane ; GO:0031307 integral component of mitochondrial outer membrane; GO:0016592 mediator complex; GO:0043209 myelin sheath; GO:0005739 mitochondrion; GO:0005759 mitochondrial matrix; GO:0030424 axon; GO:0005829 cytosol; GO:0005783 endoplasmic reticulum); biological process :( GO:0051881 regulation of mitochondrial membrane potential; GO:0090141 positive regulation of mitochondrial fission; GO:0008053 mitochondrial fusion; GO:0000266 mitochondrial fission; GO:0090200positive regulation of release of cytochrome c from mitochondria; GO:0007005 mitochondrion organization; GO:0050821 protein stabilization; GO:0043066 negative regulation of apoptotic process), and molecular function :( GO:0003924 GTPase activity; GO:0005525 GTP binding).We found that it was mainly related to the composition and function of mitochondria, and also found that it was involved in the FoxO signal pathway. FoxO signaling pathway (Fig. 4).

Table 1  
GO and KEGG information

Category	Term	Count	P-Value
CC	GO:0005741 mitochondrial outer membrane	12	8.80E-15
CC	GO:0005743 mitochondrial inner membrane	14	2.10E-11
CC	GO:0031307 integral component of mitochondrial outer membrane	7	2.90E-11
CC	GO:0016592 mediator complex	6	1.70E-06
CC	GO:0043209 myelin sheath	8	2.10E-05
CC	GO:0005739 mitochondrion	15	1.40E-04
CC	GO:0005759 mitochondrial matrix	5	7.80E-04
CC	GO:0030424 axon	5	6.10E-03
CC	GO:0005829 cytosol	12	1.70E-02
CC	GO:0005783 endoplasmic reticulum	7	4.90E-02
BP	GO:0050821 protein stabilization	6	1.60E-04
BP	GO:0043066 negative regulation of apoptotic process	5	3.80E-02
BP	GO:0051881 regulation of mitochondrial membrane potential	8	1.50E-11
BP	GO:0090141 positive regulation of mitochondrial fission	7	8.70E-11
BP	GO:0008053 mitochondrial fusion	6	1.50E-09
BP	GO:0000266 mitochondrial fission	5	4.40E-07
BP	GO:0090200 positive regulation of release of cytochrome c from mitochondria	5	1.10E-06

Category	Term	Count	P-Value
BP	GO:0007005 mitochondrion organization	5	1.90E-05
MF	GO:0003924 GTPase activity	9	1.20E-06
MF	GO:0005525 GTP binding	9	2.50E-04
KEGG_pathway	FoxO signaling pathway	5	6.00E-03

## Discussion

Breast cancer is the most common malignant tumor in women. Patients with brain metastasis of breast cancer will have neurological symptoms, poor quality of life and poor prognosis, which will bring mental and economic blow to patients and their families. Factors such as poverty and social support can affect the survival status of patients with breast cancer.<sup>[11]</sup> At present, there is still no effective systemic treatment for brain metastasis of breast cancer.<sup>[12]</sup> Therefore, it is urgent to find effective therapeutic targets.

Mitochondrial production of adenosine triphosphate (ATP), is an important element for cells to maintain life activities. In normal cells, the main pathway of ATP synthesis is oxidative phosphorylation, while in tumor cells, aerobic glycolysis is the main pathway.<sup>[13]</sup> The researchers compared the mitochondria of cancer cells and normal cells and found that the structure and function of mitochondria were different.<sup>[14]</sup> The proliferation of cancer cells requires the synthesis of macromolecular substances such as DNA and proteins.<sup>[15]</sup> The proliferation of cancer cells will change their metabolism, when the value is out of control, it will invade the surrounding tissue, survive in the human circulatory system and settle in other organs.<sup>[15.16.17]</sup> Cell dedifferentiation is the process of occurrence and development of cancer, and mitochondria play an important role in this process. Inhibiting the function of mitochondria can inhibit the growth of tumor cells.<sup>[18]</sup> The targeted action of drugs on the mitochondria in tumor cells can produce a certain anti-tumor effect.<sup>[19]</sup> E2F1 may enter the cytoplasm through mitochondria and affect the cell cycle regulation of Hepatocellular Carcinoma.<sup>[20]</sup> C-Myc promotes the development of hepatocellular carcinoma by inducing excessive mitochondrial-endoplasmic reticulum coupling.<sup>[21]</sup> In breast cancer, long chain fatty acid aromatic urea can reduce the activity of MDA-MB-231 breast cancer cells through mitochondrial targeting.<sup>[22]</sup> The researchers found that mitochondrial division inhibitor-1 (Mdivi-1) inhibits the migration of MCF7 cells by inhibiting mitochondrial-related functions.<sup>[23]</sup> It can be found that the function of mitochondria is closely related to the production and development of tumor cells. Our study found that OPAI and its associated genes are closely related to the composition and function of mitochondria, among which the related components involved in mitochondrial cells are GO:0005741

mitochondrial outer membrane; GO:0005743 mitochondrial inner membrane; GO:0031307 integral component of mitochondrial outer membrane; GO:0005739 mitochondrion; GO:0005759 mitochondrial matrix and GO:0005783 endoplasmic reticulum; molecular function(GO:0003924 GTPase activity; GO:0005525 GTP binding). (GO:0051881 regulation of mitochondrial membrane potential; GO:0090141 positive regulation of mitochondrial fission; GO:0008053 mitochondrial fusion; GO:0000266 mitochondrial fission; GO:0090200 positive regulation of release of cytochrome c from mitochondria; GO:0007005 mitochondrion organization) is involved in the process of mitochondrial biology.

Mediator complex (MED) is a component of eukaryotic RNA polymerase II, which transmits the signal of transcriptional activator and participates in the beginning of transcription.<sup>[24]</sup>The subunit of Mediator complex is involved in a variety of biological processes and is related to the occurrence and development of human cancer.<sup>[25]</sup>Kim found that a decrease in the number of MED1 can increase the probability of cell metastasis in tumor models and in the human body.<sup>[26]</sup>Nagpal reports that MED1/ER- $\alpha$  / miR-191 axis can promote the proliferation and migration of breast cancer cells.<sup>[27]</sup> Joseph found that MED7 was associated with the prognosis of invasive lobular carcinoma of the breast.<sup>[28]</sup>Wang found that MED15 may be used as a biomarker to predict the overall survival of hepatocellular carcinoma.<sup>[29]</sup>In addition, it was found that MED19 was involved in the transcriptional regulation of almost all RNA polymerase II.<sup>[30]</sup>Lewis found that MED19 can regulate the proliferation and metastasis of tongue cancer cells, while destroying MED19 has anti-tumor effect.<sup>[31]</sup>Zhang found that MED19 can enhance the proliferation, epithelial-mesenchymal transformation, invasion and migration of breast cells in vivo and in vitro.<sup>[32]</sup>Shi found that knocking down the expression of MED23 can inhibit the proliferation and metastasis of non-small-cell lung carcinoma (NSCLC) cells.<sup>[33]</sup>Wang found that MED27 can promote the bad behavior of breast cells.<sup>[34]</sup>These results suggest that MED participates in a wide range of human biological behaviors and plays an important role in the occurrence and development of cancer. Our study found that there is an interaction between OPA1 and MED9, MED16, MED20 MED22, MED23, MED27, MED30. OPA1 may affect the related functions of the Mediator complex.

We found that FOXO signaling pathway is involved in cell cycle regulation, apoptosis, phagocytosis, oxidative stress resistance antioxidant stress, DNA repair, metabolism, immunomodulatory and muscular atrophy. The proliferation of cancer cells needs to consume a lot of energy and produce more reactive oxygen species (ROS) to promote the development of the disease.<sup>[35]</sup>FOXO protein has the ability to degrade ROS. Down-regulation of FOXO can lead to the increase of ROS in vivo and promote the progression of tumor.<sup>[36]</sup>FOXO protein can affect PI3K/AKT pathway, and lead to malignant transformation of epithelial tissue.<sup>[37]</sup>Many human cancers are associated with the activation of PI3K/AKT pathway.<sup>[38]</sup>Increased activity of PI3K/AKT signaling pathway is associated with poor prognosis in patients with breast cancer.<sup>[39,40]</sup>Shan found that CTCF affects the progress of prostate cancer by regulating FoxO signal pathway.<sup>[41]</sup>In MCF7 human breast cancer cell line, FOXO1 can affect cell proliferation.<sup>[42]</sup>Zhang found that HDAC3-FoxO3 complex can promote the metastasis of breast cancer cells.<sup>[43]</sup> All these suggest that FOXO signal pathway may be involved in the distant metastasis of

breast cancer cells. Our study found that OPA1 and its related genes are involved in the FOXO signal pathway and further participate in the distant metastasis of breast cancer.

## Conclusion

OPA1 may act on mitochondrial-related regulatory genes, cause changes in the structure and function of mitochondria, act on the Mediator complex, participate in the synthesis of biological macromolecules needed by cancer cells, and affect the FOXO signal pathway. These effects together lead to the occurrence of brain metastasis of breast cancer, so OPA1 is a potential targeted therapy for the prevention and treatment of brain metastasis of breast cancer, but it still needs to be further studied.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

YES

### Availability of data and materials

The datasets generated and analysed during the current study are available in the GEO dataset repository, [<https://www.ncbi.nlm.nih.gov/geo/>]

### Competing interests

The authors declare that they have no competing interests

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### Authors' contributions

Kanghua Huang writing, Xueying Luo and Qiuyi Guo providing language, Jinsong He writing assistance, Feng Li, Rui Gao, Zihan Zhou proofreading the article. All authors read and approved the final manuscript

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Not applicable

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## Figures

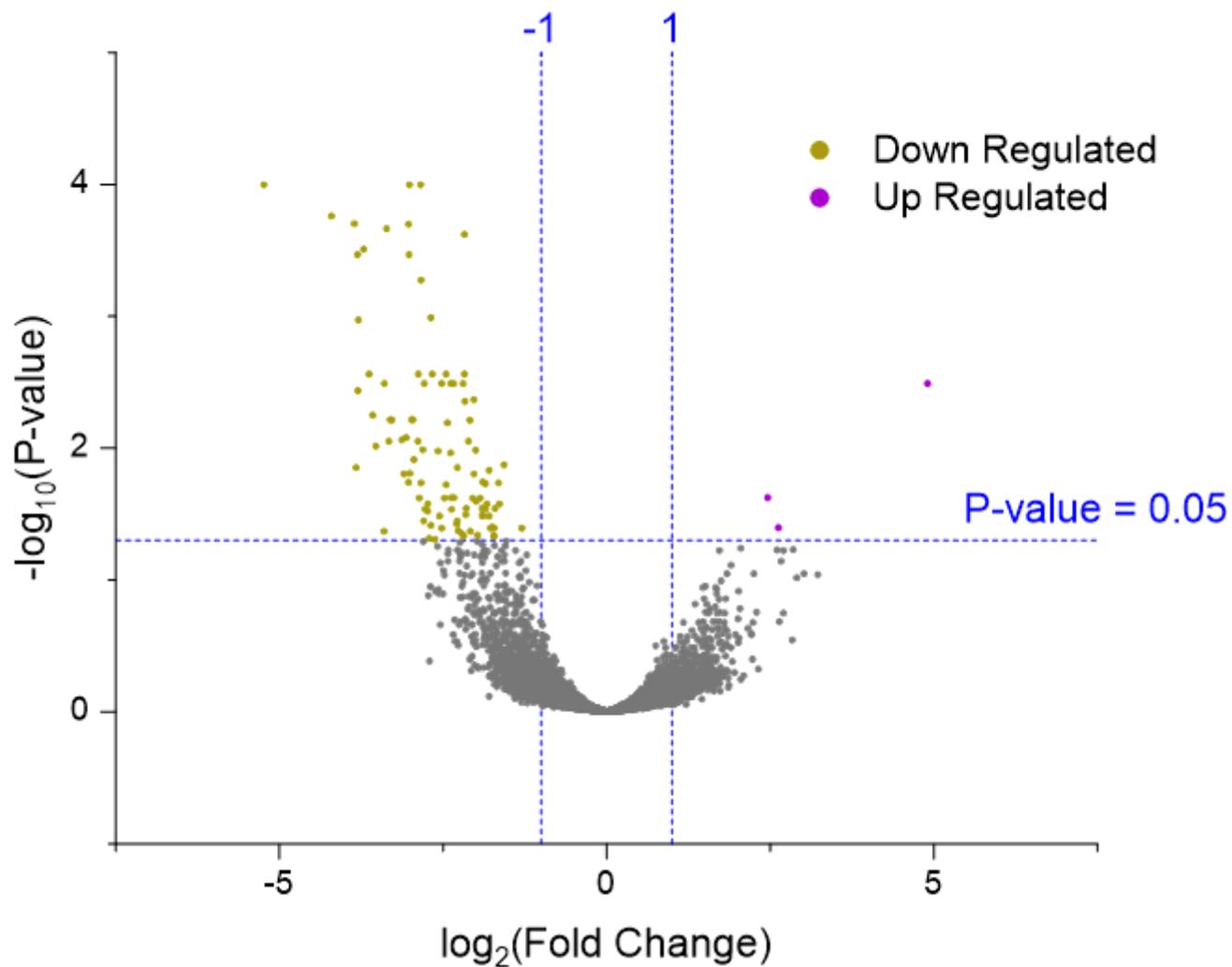


Figure 1

Volcanic map of differential genes

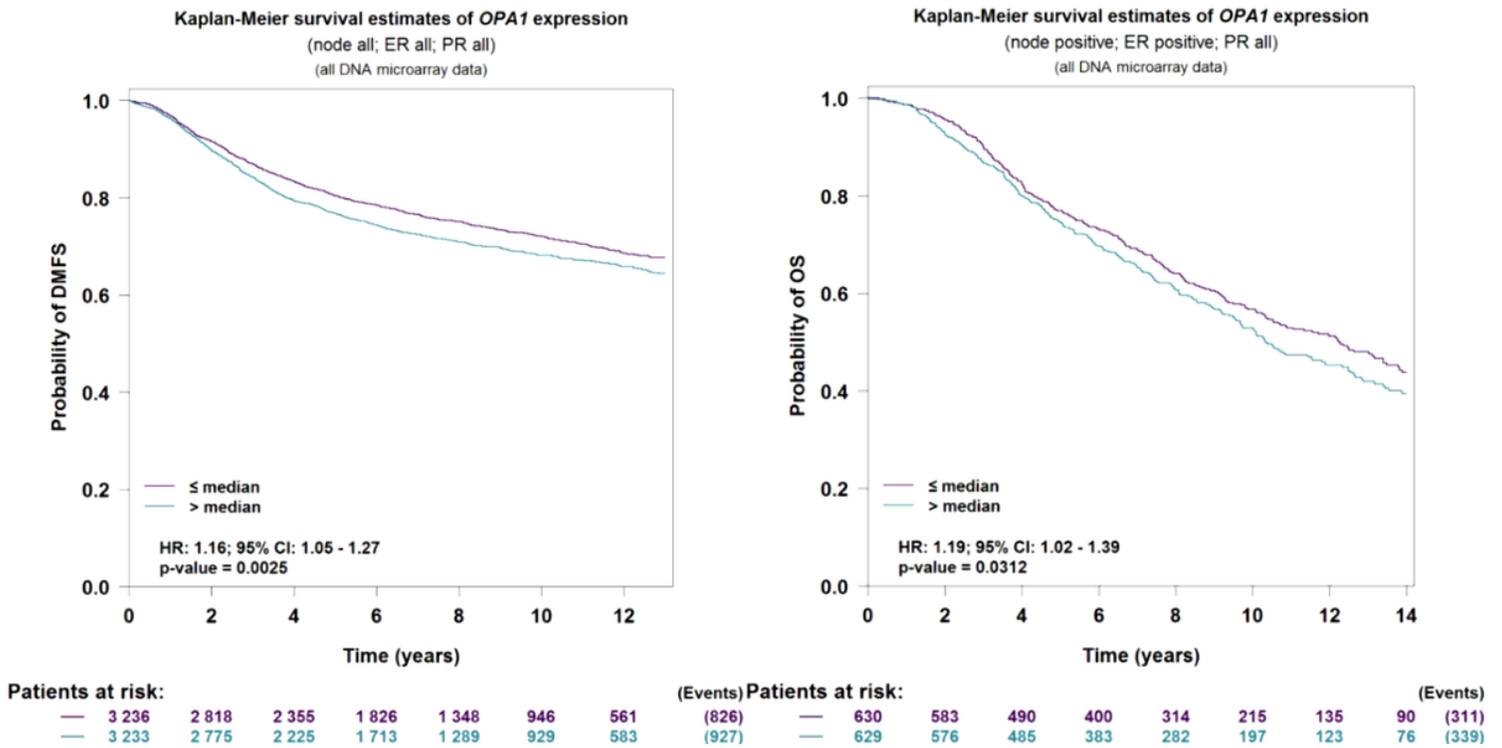


Figure 2

DMFS and OS of OPA1 in breast cancer patients



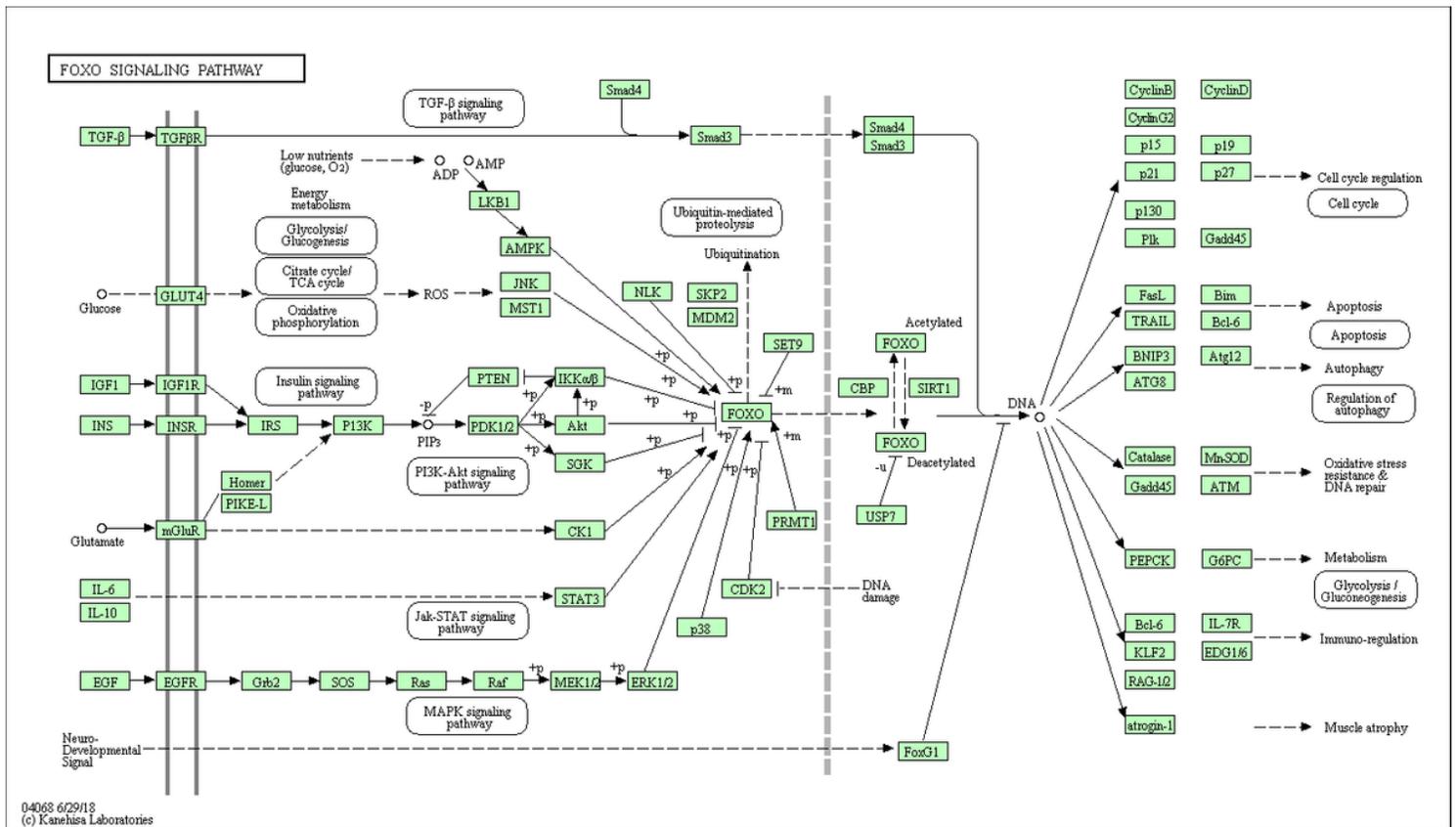


Figure 4

FOXO signaling pathway