Glioblastoma

Group 2:
The Group Leadah Team

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MIRcore

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01 Glioblastoma Background

Definition:

Glioblastoma is a fast-growing type of central nervous system tumor that affects the brain and spinal cord. Glioblastoma usually occurs in adults and is more concentrated in the brain. Glioblastoma is a type of glioma, the umbrella term for brain cancer.

300,000

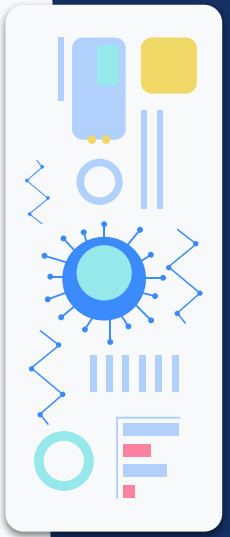
More than 300,000 people are diagnosed with Glioblastoma every year globally, making it the most common brain cancer

Morgan’s Story:

Morgan was a normal, healthy, very happy 5-year old girl when she was diagnosed with a Glioblastoma Multiforme brain tumor in December of 1997. She’d had no real outward symptoms and her diagnosis was utterly incomprehensible. Morgan’s parents were told that GBMs were very rare in children and that Morgan likely had only a 15% chance of surviving this tumor. Morgan bravely battled her cancer and she shined through it all, never complaining. She had 3 surgeries, several rounds of high-dose chemotherapy, a ‘stint’ on the Bone Marrow Transplant Unit, a bout of RSV and an endless parade of blood transfusions. She got to go to first grade. Despite their decision to aggressively treat her cancer, there was nothing left that Morgan’s parents could try. They spent her last few months quietly – with friends and family who had walked that road with them. Morgan died peacefully and at home on November 7th, 1998, at the age of 6. (Morgan Adams Foundation)

Symptoms

- Headaches
- Seizures
- Vomiting
- Drowsiness
- Changes in personality
- Weakness on one side of the body
- Memory loss
- Speech difficulty
- Changes in vision
- Memory and language problems
- Issues with coordination
- Issues with speech
- Issues with hearing
- Vision problems



Diagnosing Glioblastoma

- Physical exam identifying symptoms and using imaging tests like CT and/or MRI scans
  - “Gold standard” for glioblastoma imaging
  - Help diagnose, locate, and determine the size of the cancer

- Neurologic exams are used to check vision, hearing, balance, coordination, strength and reflexes
  - Problems help diagnose the brain with Glioblastoma

Causes

- No specific cause, but multiple risk factors
- Factors associated with glioblastoma:
  - Decreased susceptibility to allergy and impaired immune response
  - Hereditary cancer syndromes including Li-fraumeni syndrome and Lynch syndrome

02 Methodology

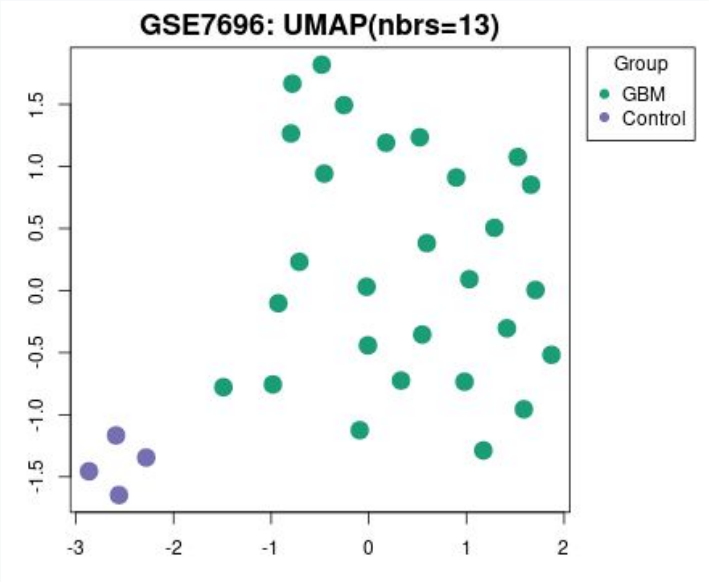
Research Question:

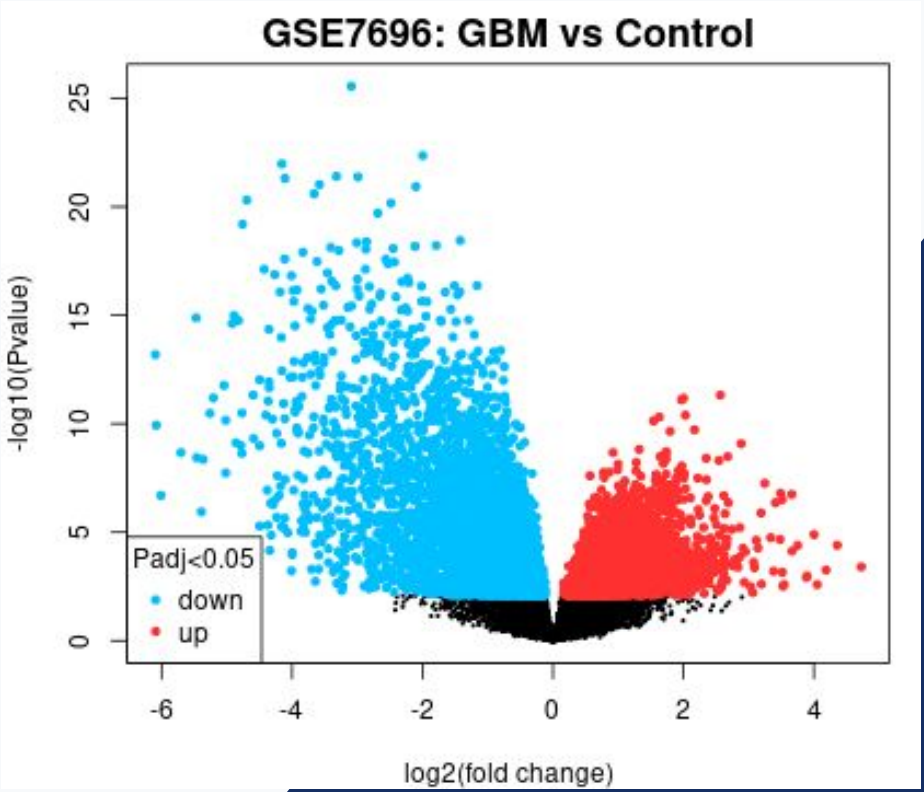
What impact do the upregulation of certain genes in the ECM pathway have on the development of Glioblastoma?

GSE7696 – Dataset

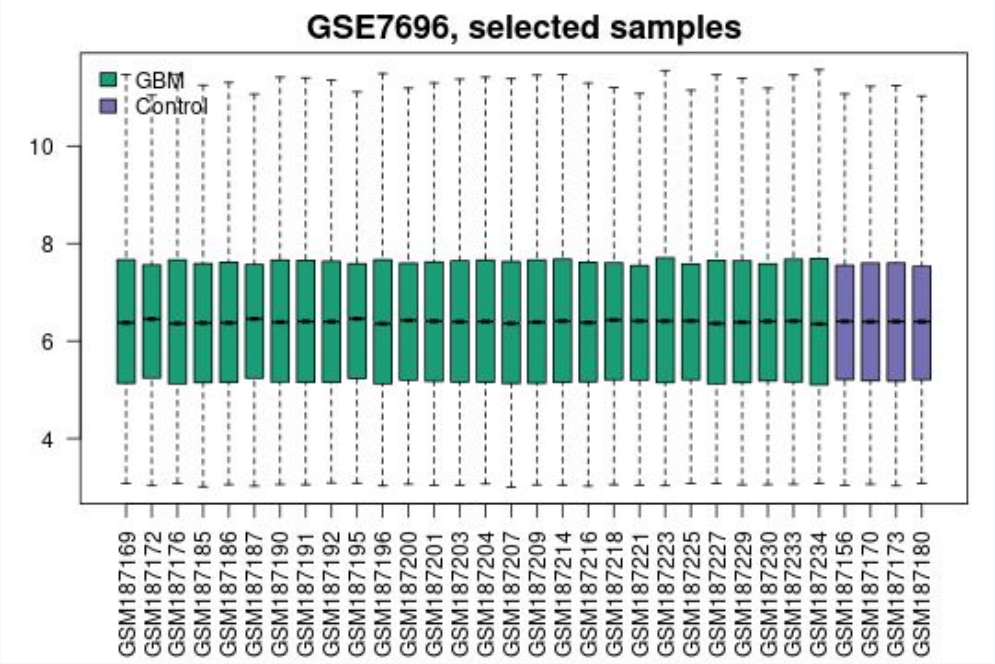
- The dataset consisted of 84 samples and was most recently updated in 2023
- 80 patients with Glioblastoma, and 4 “normal” brain tissue samples
- The data was used to identify factors of a resistance to chemoradiation therapy
- We chose to compare the non-tumoral samples and the patients treated with radiotherapy for GBM
    - Total of 28 patients with GBM treated with radiotherapy

GSE7696 Graphs



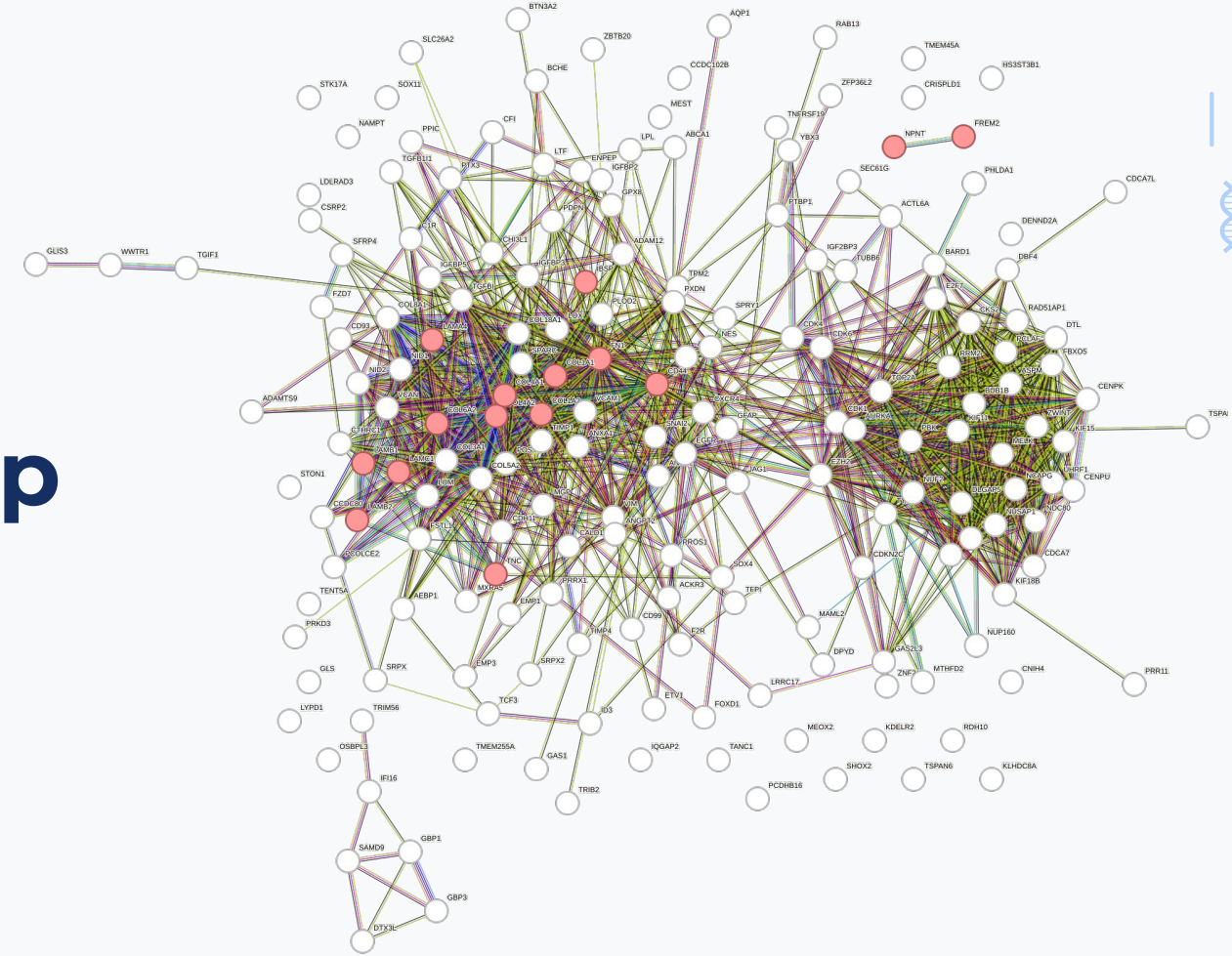


GSE7696 Graphs



String Map

Top 250 upregulated genes in glioblastoma and their connections to each other



String Pathway

Reference publications (PubMed)

publication	(year) title	count in network	strength	false discovery rate
PMID:34238152	(2022) KIAA0101 in Malignant Pleural Mesothelioma: A Pot...	6 of 6	2.02	3.63e-06
PMID:17938213	(2008) Fibrotic response as a distinguishing feature of resis...	6 of 6	2.02	3.63e-06
PMID:38339384	(2024) Identification of Hypoxia Prognostic Signature in Glio...	5 of 5	2.02	5.27e-05
PMID:32401038	(2020) Key Genes Associated with Prognosis and Tumor Infi...	5 of 5	2.02	5.27e-05
PMID:21764694	(2011) [Investigation of mRNA expression of collagen gene...	5 of 5	2.02	5.27e-05

(more ...)

Local network cluster (STRING)

cluster	description	count in network	strength	false discovery rate
CL:19474	Fibrillar collagen, C-terminal	4 of 5	1.92	0.00018
CL:6622	Mixed, incl. Mitotic centrosome separation, and Nuclear mic...	4 of 7	1.77	0.00044
CL:19654	laminin-1 complex, and G2 nidogen domain and fibulin	4 of 7	1.77	0.00044
CL:6620	Mixed, incl. Spindle elongation, and Axon hillock	6 of 12	1.72	2.63e-06
CL:19471	Banded collagen fibril	5 of 10	1.72	3.90e-05

(more ...)

KEGG Pathways

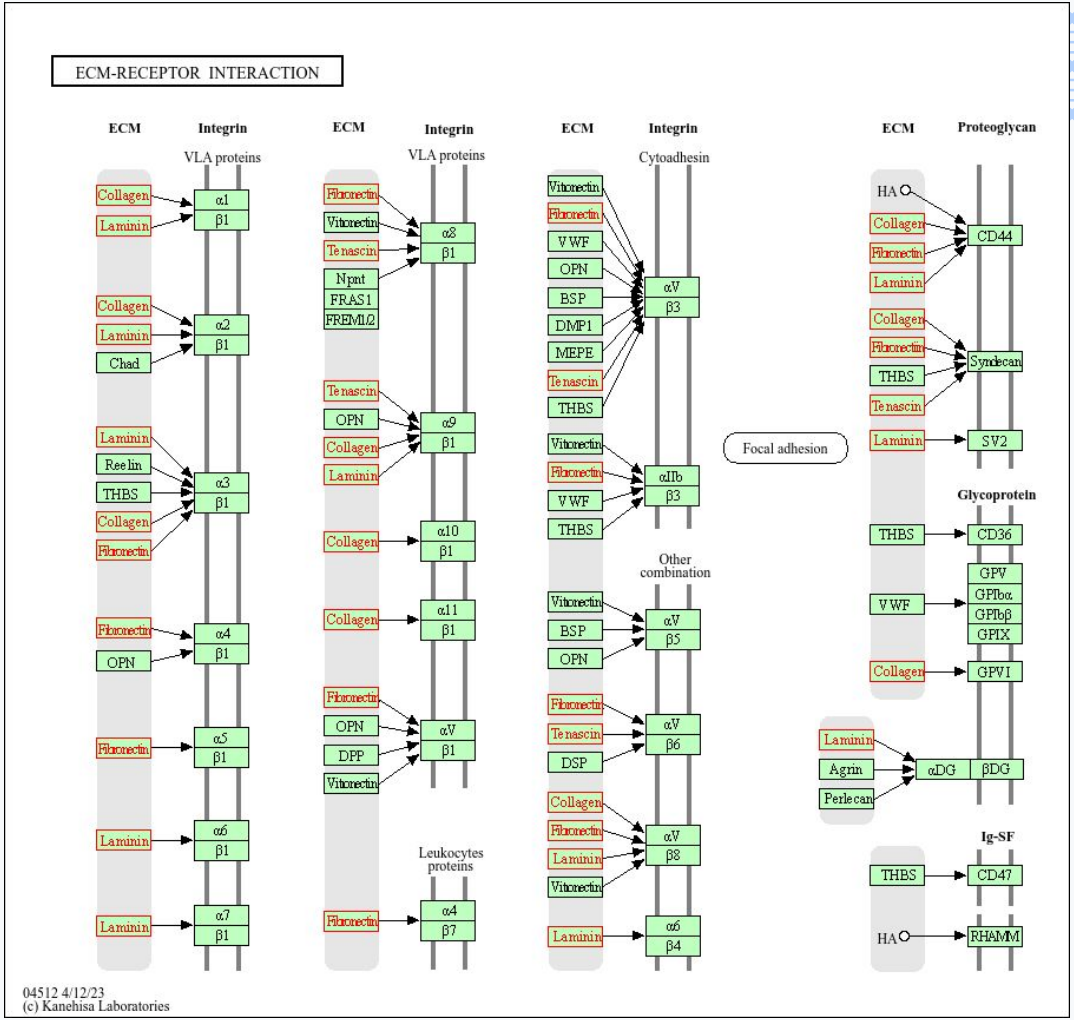
pathway	description	count in network	strength	false discovery rate
hsa04512	ECM-receptor interaction	15 of 88	1.25	1.76e-11
hsa05222	Small cell lung cancer	10 of 92	1.05	5.30e-06
hsa05146	Amoebiasis	10 of 101	1.01	7.00e-06
hsa04974	Protein digestion and absorption	9 of 100	0.97	4.72e-05
hsa04933	AGE-RAGE signaling pathway in diabetic complications	8 of 96	0.94	0.00028
hsa04115	p53 signaling pathway	5 of 72	0.86	0.0255
hsa04510	Focal adhesion	13 of 195	0.84	7.00e-06
hsa04610	Complement and coagulation cascades	5 of 82	0.8	0.0374
hsa05165	Human papillomavirus infection	18 of 324	0.76	8.31e-07
hsa05206	MicroRNAs in cancer	8 of 159	0.72	0.0067
hsa04110	Cell cycle	6 of 120	0.72	0.0365
hsa04151	PI3K-Akt signaling pathway	17 of 349	0.71	7.00e-06
hsa04926	Relaxin signaling pathway	6 of 126	0.7	0.0397
hsa05200	Pathways in cancer	15 of 515	0.48	0.0064

(less ...)

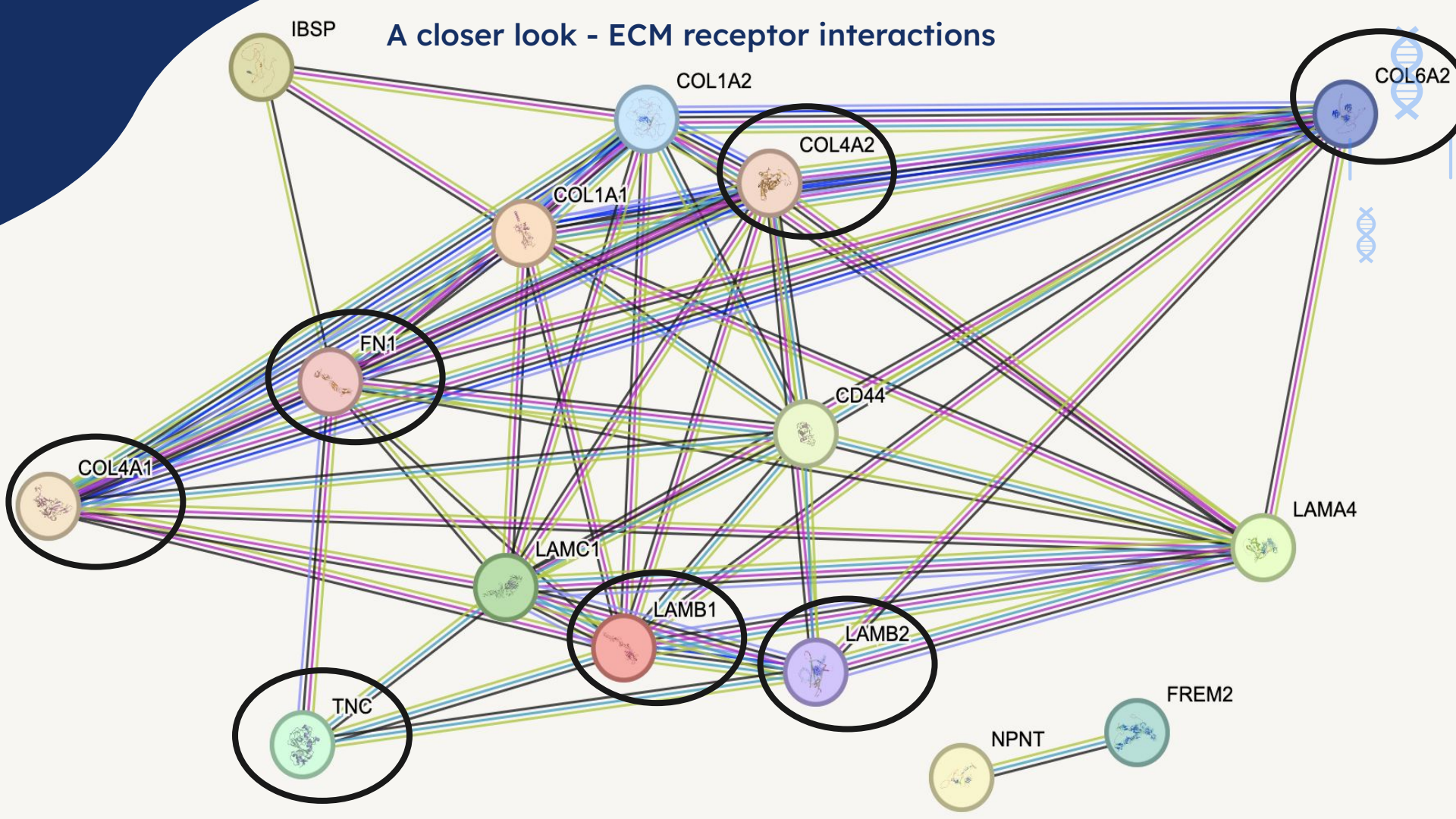
Reactome Pathways

pathway	description	count in network	strength	false discovery rate
HSA-8854521	Interaction between PHLDA1 and AURKA	2 of 2	2.02	0.0264
HSA-9632700	Evasion of Oxidative Stress Induced Senescence Due to Def...	2 of 3	1.84	0.0411

KEGG ECM Pathway



A closer look - ECM receptor interactions

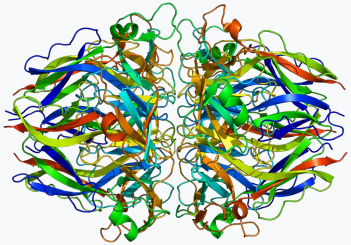


Our Focus Genes

COL4A1 COL4A2 LAMB1 FN1

COL6A2 LAMB2 TNC

GENES - COL4A1



Function

Encodes type IV collagen alpha proteins, which are integral components of basement membranes.

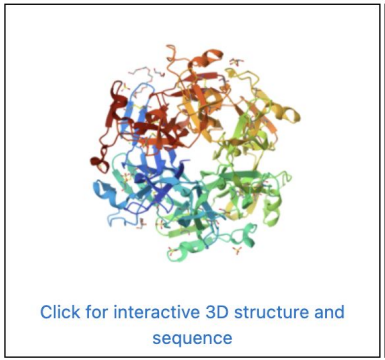
Disorders

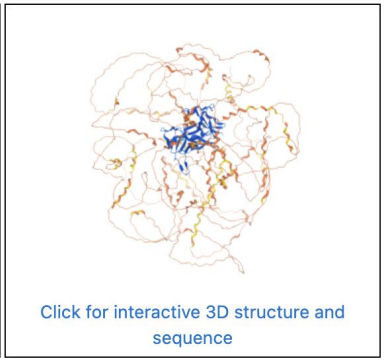
Linked to Alport syndrome and cerebrovascular disease, highly upregulated in glioblastoma (logFC value ~3)

Drugs

- Collagenase clostridium histolyticum
- Ocriplasmin
- D-Tyrosine (possibly)

GENES - COL4A1





Model Confidence:
- Very high (pLDDT > 90)
- Confident (90 > pLDDT > 70)
- Low (70 > pLDDT > 50)
- Very low (pLDDT < 50)

LogFC: 3.41038386
P-value: 0.000000441
Chromosome Location: 13q34

GENES - COL4A2

Function

- Encodes one of the six subunits of type IV collagen,
- Major structural component of basement membranes.
- Protein-coding gene

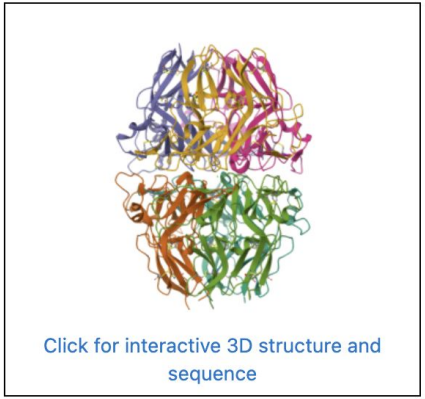
Disorders

- Brain Small Vessel Disease
- Cerebral Palsy
- Familial Porencephaly
- Hemorrhage, Intracerebral

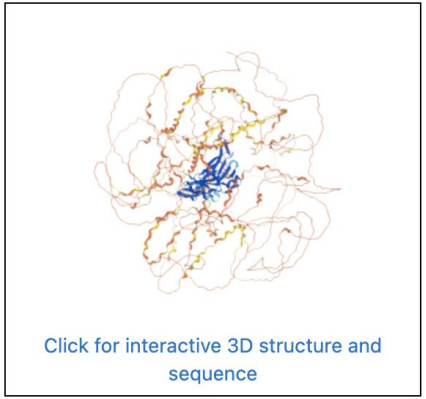
Drugs

- Collagenase clostridium histolyticum
- Ocriplasmin
- Navoximod

GENES - COL4A2



Click for interactive 3D structure and sequence



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Model Confidence:
- Very high (pLDDT > 90)
- Confident (90 > pLDDT > 70)
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- Very low (pLDDT < 50)

LogFC w3: 1.47993571
P-value: 9.28E-04
Chromosome Location: 13q34

GENE - LAMB1

Functions

- Binds cell membranes together through the protein Laminin
- Mediates the attachment, migration and organization of cells during development

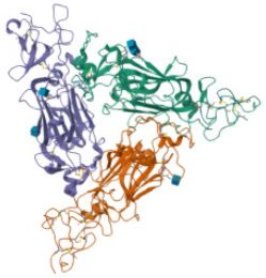
Disorders

- The gene **LAMB1** is associated with Embryonic Carcinoma and Teratocarcinoma which are different types of Cancers

Drugs

- Ocriplasmin is used to help mediate this gene
- Job is to down regulate the production of Laminin
- To much Laminin produced would causeover binding of adjacent cells and cell membranes

GENES - LAMB1



Click for interactive 3D structure and sequence

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Model Confidence:
- Very high (pLDDT > 90)
- Confident (90 > pLDDT > 70)
- Low (70 > pLDDT > 50)
- Very low (pLDDT < 50)

LogFC: 2.66685111
P-value: 1.65E-03
Chromosome Location: 7q22

GENES - FN1

Function

- Fibronectin 1 (FN1) is involved in binding muscle, healing wounds, blood coagulation, and working with bone material

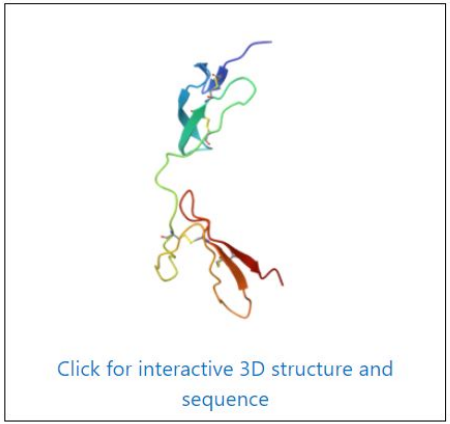
Disorders

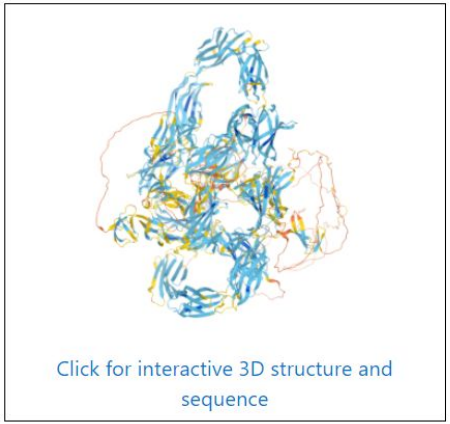
- Diseases associated with FN1 include types of Dysplasia (problems in the bones and chronic pain) and Corner Fractures (injuries to the ends of bones)

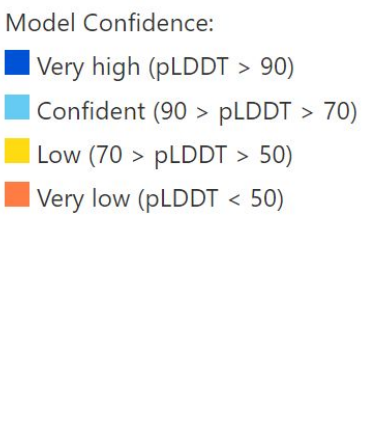
Drugs

- Drugs: The drug Ocriplasmin is an enzyme that works in the muscles to combat muscle problems.

GENES - FN1







LogFC: 2.41333882
P-value: 1.81E-05
Chromosome Location: 2q35

GENES - COL6A2

Functions

It encodes one of the three alpha chains of type VI collagen, a beaded filament collagen found in most connective tissue.

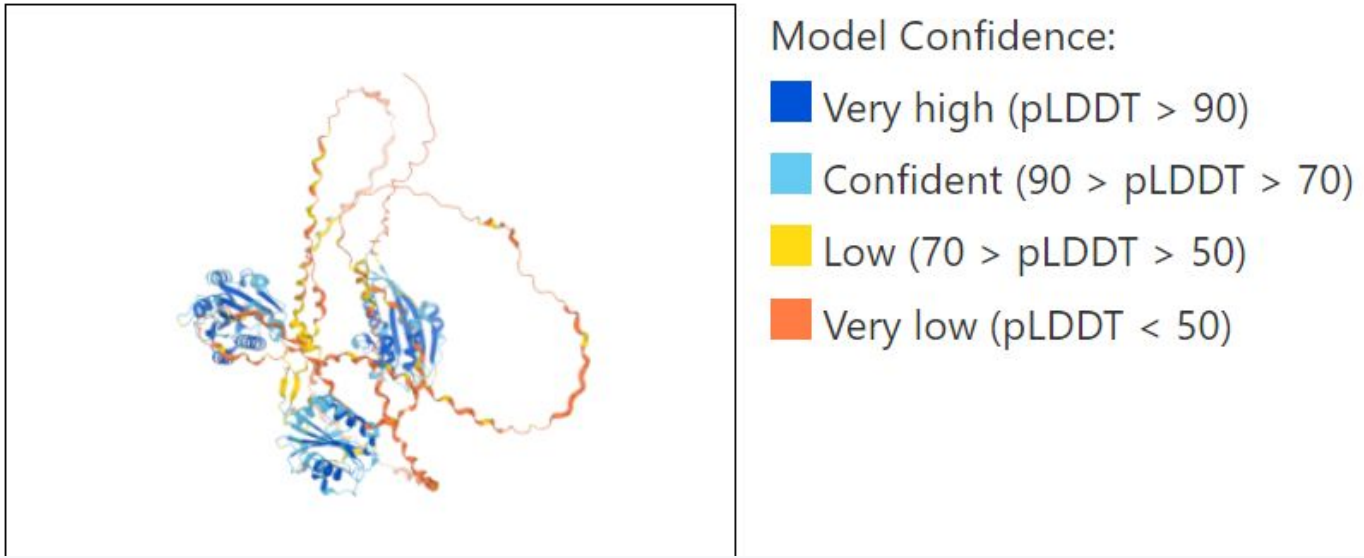
Disorders

Myosclerosis (Autosomal Recessive)

Drugs

Collagenase clostridium histolyticum, and Ocriplasmin

GENES - COL6A2



LogFC: 2.03564757
P-value: 1.17E-02
Chromosome Location: 21q22.3

GENES - LAMB2

Function

- Mediates the attachment, migration and organization of cells into tissues

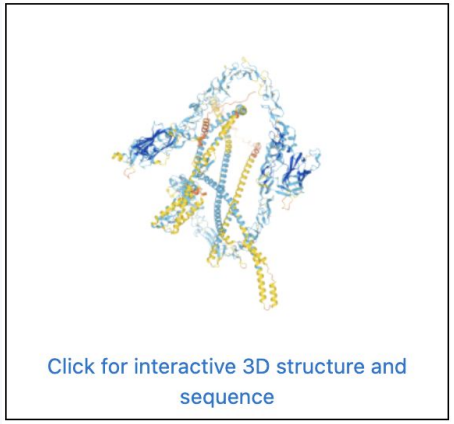
Disorders

- Pierson Syndrome
- Nephrotic Syndrome
- Myasthenic Syndrome
- Kidney disease

Drugs

- Acetylcholine
- Heparin
- Bovine
- Calcium
- Tripeptide
- Ocriplasmin

Genes - LAMB2



Model Confidence:
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- Confident (90 > pLDDT > 70)
- Low (70 > pLDDT > 50)
- Very low (pLDDT < 50)

LogFC: 1.93837854
P-value: 0.00000142
Chromosome Location: 3p21

GENES - TNC

Functions

Encodes an EMP (extracellular matrix protein) with restricted tissue distribution

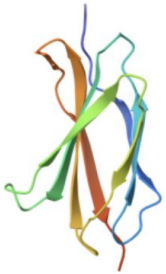
Disorders

- Deafness
- Bullous Keratopathy
- Acute Myocarditis
- Tendinopathy

Drugs

- Dactinomycin
- Dexamethasone
- Diethylstilbestrol
- Chloramphenicol
- Ocriplasmin

GENES - TNC



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Model Confidence:
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- Confident (90 > pLDDT > 70)
- Low (70 > pLDDT > 50)
- Very low (pLDDT < 50)

LogFC: 3.07616782
P-value: 2.44E-04
Chromosome Location: 9q33

03 Hypothesis

Hypothesis:

A probable cause of Glioblastoma is the upregulation of genes within the ECM pathway.

Treatment/Next Steps

Surgery/Radiation

- Surgery is generally the first course of action, but can not always be performed due to the tumor location

- Radiation Therapy is used to target the site of the respected tumor to prevent the tumor from recurring

Treatment

Ocriplasmin

- Ocriplasmin
- Many genes within the ECM pathway are involved with the production of Laminin
- Upregulation of genes that produce the protein Laminin will cause abnormal binding and growth of cells, which will create abnormal masses to form within the affected tissue (AKA Tumors)
- Down regulation of upregulated Laminin

LIMITATIONS

- Sample sizes
- Location of the tumor
- Small amount of control patients
- Time

David’s Success Story

When David was ten, he was diagnosed with glioblastoma in his right temporal lobe. He has always been a fighter and after going through thirty three radiation treatments and a year of chemotherapy, his tumor went away. Sadly, a year later, David’s tumor was back in the same location. David was eleven and a half years old by now and his parents decided to try surgery. The surgery was a success, however David was still given only three months left to live. Still determined, David’s parents brought him to The Duke Tumor Center in North Carolina to get his chemo protocol. His parents are very happy to report that David will be eighteen in October 2010 and remains cancer free! He has had quite a journey, home schooling, growth hormones and forever on synthroid due to radiation near the thyroid—but he has persisted through all of it. His motto is to never give up! There is always hope!

Conclusion

Based on our results we can confirm that a probable cause of Glioblastoma is the upregulation of genes within the ECM pathway, and that Ocriplasmin is a widespread drug used to treat many factors of Glioblastoma

Research References

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- https://www.sciencedirect.com/science/article/abs/pii/B9780444634863000050#:~:text=During%20central%20nervous%20system%20development,between%20pre%2D%20and%20postsynaptic%20cells
- https://string-db.org/cgi/network?taskId=bckL3wL1dlHI&sessionId=bpeXGZrWpzs9
- https://www.nicklauschildrens.org/news-and-events/patient-stories/david-glioblastoma

Thank You!
Questions?