

Network Analysis-Based Drug Repositioning for Glioblastoma

Erin McGowan¹, Qian Zhu¹

¹Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20850



Abstract

- Glioblastoma is a malignant (cancerous) brain tumor that develops from specific types of brain cells called astrocytes and oligodendrocytes. Glioblastoma are often very aggressive and grow into surrounding brain tissue.¹
- Currently treatment options for glioblastoma are extremely limited and rely on surgery and chemotherapy rather than less potentially less invasive drug therapies².
- We present a preliminary, network analysis-based approach to drug repositioning candidate discovery for glioblastoma, an approach chosen due to the ability of drug repositioning to dramatically reduce research costs and shorten the drug development timeline.
- We have developed a Glioblastoma-Based Network (GBN) by integrating information extracted from the NCATS GARD Knowledge Graph (NGKG)³.
- A variety of network analysis measures, namely degree, closeness, betweenness, PageRank, and eigenvector centrality, have been calculated to identify high-influence nodes in the GBN that could shed insight on potential drug repositioning candidates for glioblastoma.
- We substantiate our findings with evidence from PubMed⁴, and suggest further experimental evaluation for the top candidates.

Methods

Begin with the NCATS GARD Knowledge Graph (NGKG)³, which contains data related to diseases, genes, phenotypes, drugs/treatments, etc.

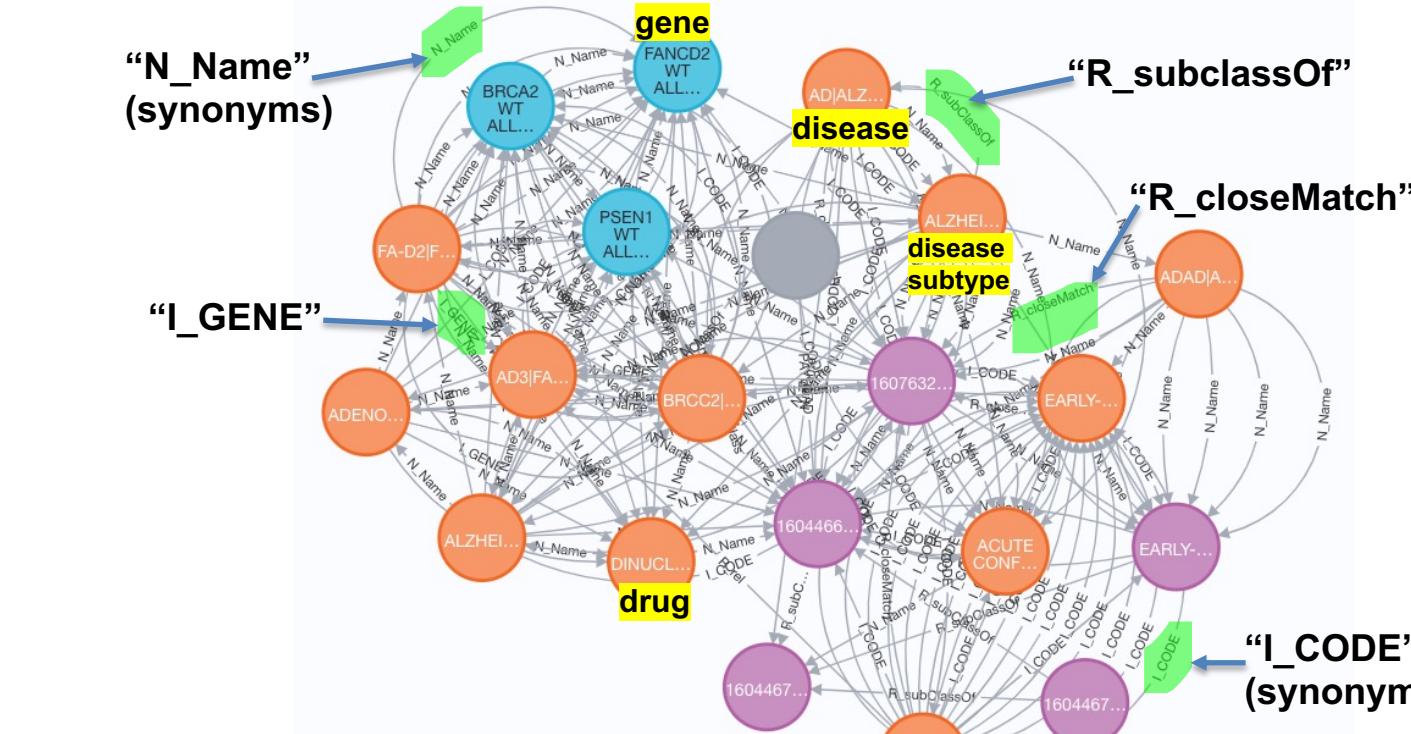


Fig 1. One of the 92 disease-based subgraphs of NGKG³ (Familial Alzheimer Disease).

Extract subgraphs from NGKG³, each containing one of the 92 diseases in the glioblastoma cluster and all nodes connected to it by a path length of up to length 3. Take the union of these subgraphs to create GBN.

Merge duplicates, resulting in nodes that contain very closely related diseases, genes, proteins, and treatments/drugs/compounds.

Identify top 10 high-influence nodes in GBN by 5 centrality measures (degree, closeness, betweenness, PageRank, and eigenvector centrality).

Divide graph into modularity classes and identify top 10 high-influence nodes in each modularity class by centrality measures.

Rank top 10 most influential nodes and substantiate connection to glioblastoma using PubMed⁴.

Acknowledgements

This project was supported by the Division of Preclinical Innovation at the National Center for Advancing Translational Sciences (NCATS) and was conducted while one of the authors, Erin McGowan, was a Data Science Fellow through Coding it Forward. Special thanks to Jaleal Sanjak for sharing the glioblastoma-based rare disease cluster and Iyanuoluwa Odebode for valuable suggestions on network analysis.

Results

Network Property	Results
Nodes	1466
Edges	107423
Average Degree	73.276
Net Diameter	10
Average Path Length	3.751
Graph Density	0.05
Modularity Classes	41

Table 1. GBN network properties.

Top 10 Largest Modularity Classes		
Index	Description	% of Nodes
1	Movement disorders	14.26
2	Amyotrophic Lateral Sclerosis and Related Conditions	10.64
3	Leukodystrophies and Related Conditions	9.55
4	Seizures/Epilepsies	9
5	Parkinsonism, Progressive Supranuclear Palsy, Dementia, and Related Conditions	6.41
6	Encephalopathies and Related Conditions	5.53
7	Nervous System Conditions	5.12
8	Cerebrovascular Conditions	5.12
9	Prion Diseases	4.84
10	Neurodegeneration with Brain Iron Accumulation and Dystonias	4.43

Table 2. Descriptions of the 10 largest modularity classes.

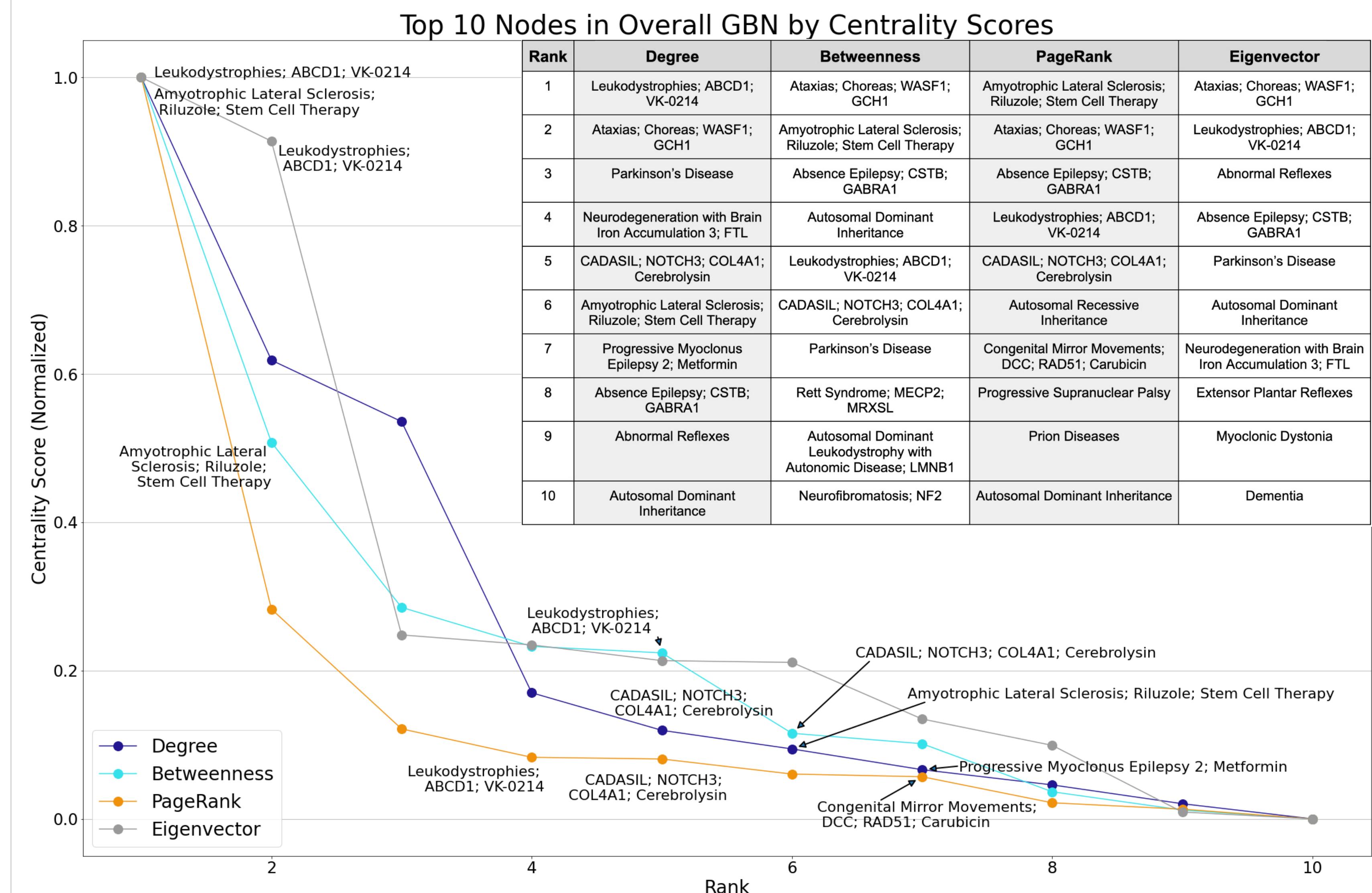


Fig 2. The top 10 most influential nodes in the overall GBN by degree, betweenness, eigenvector, and PageRank centralities. Nodes highlighted in the conclusion section are labeled on plot.

Top 10 Overall Nodes	
1	<ul style="list-style-type: none"> Ataxias, Chores SETX, WASF1, GCH1 genes
2	<ul style="list-style-type: none"> Leukodystrophies ABCD1, ABC42, AMN, ACOX1, ECK2921, ECK1408 genes VK-0214
3	<ul style="list-style-type: none"> Absence Epilepsy CSTB, GABRA1, EC1 genes
4	<ul style="list-style-type: none"> Amyotrophic Lateral Sclerosis (ALS) ALS1, ALS2, IGFALS genes Riluzole, THC, Stem Cell Therapy
5	<ul style="list-style-type: none"> Parkinson's Disease FBXO7, DCTN1, GBA, PARK1, PARK2, PARK5, PARK6, PARK7, PARK8 genes
6	<ul style="list-style-type: none"> CADASIL Syndrome NOTCH3, COL4A1, HTRA1 genes Cerebroylsin, Palm Tocotrienol Complex
7	<ul style="list-style-type: none"> Neurodegeneration with Brain Iron Accumulation 3 (NBIA3) FTL gene
8	<ul style="list-style-type: none"> Progressive Myoclonus Epilepsy 2 (PME2) EPM2A, EPM2B genes Metformin
9	<ul style="list-style-type: none"> Congenital Mirror Movement Disorder (CMM) MRMV1, MRMV2, MRMV3 genes Carubicin
10	<ul style="list-style-type: none"> Rett Syndrome MECP2, MRXSL genes

Table 3. The top 10 overall most influential nodes in the GBN.

Conclusions

- Overall • Top 10 nodes all contain central nervous system (brain or neurodegenerative) conditions
• Many nodes in top 10 are genetic disorders, several are X-linked
- Gene • Novel COL4A1 gene variant recently found to be associated with glioblastoma⁵
• NOTCH3 is a prognostic factor that promotes glioma cell proliferation, migration, and invasion⁶
• RAD51 expression levels are inversely correlated with glioblastoma patient survival⁷
- Drug • Metformin (PME2) reduces the proliferation rate of tumor-initiating cell-enriched cultures isolated from glioblastomas⁸
• Riluzole (ALS) pretreatment sensitizes glioma to radiation therapy and has synergistic effects with select other drugs when used to treat glioblastoma⁹
• Stem cell transplantation has shown potential for treating neuron and glial cell damage from glioblastoma¹⁰
• VK-0214 (currently in Phase I clinical trial as treatment for X-ALD) and could potentially be a novel candidate for glioblastoma treatment¹¹

- Experimental validation of Metformin, Riluzole, VK-0214, and stem cell transplants for glioblastoma
• While our method of merging duplicate nodes allowed us to treat very closely related conditions, genes, and treatments as one entity, parsing these could provide more granular insights
• Other methods of analyzing the GBN (different centrality measures, perturbation)

References

- ¹Glioblastoma, <https://rarediseases.info.nih.gov/diseases/2491/glioblastoma>
- ²Fisher, J. P., & Adamson, D. C. (2021). Current FDA-Approved Therapies for High-Grade Malignant Gliomas. *BioMedicine*, 9(3), 324. <https://doi.org/10.3390/biomedicines9030324>
- ³Zhu Q, Nguyen DT, Grishagin I, Southall N, Sid E, Paiser A, *An Integrative Knowledge Graph for Rare Diseases, derived from the Genetic and Rare Diseases Information Center (GARD)*. *J Biomed Semant* 11, 13 (2020).
- ⁴U.S. National Library of Medicine. (n.d.). *PubMed*. National Center for Biotechnology Information. Retrieved July 21, 2022, from <https://pubmed.ncbi.nlm.nih.gov/>
- ⁵Muto, K., Miyamoto, R., Terasawa, Y., et al. A novel COL4A1 variant associated with recurrent epistaxis and glioblastoma. *Hum Genome Var* 8, 18 (2021). <https://doi.org/10.1038/s41439-021-00150-0>
- ⁶Alqudah, M. A., Agarwal, S., Al-Kelani, M. S., Sibenaller, Z. A., Ryken, T. C., & Assem, M. (2013). NOTCH3 is a prognostic factor that promotes glioma cell proliferation, migration and invasion via activation of CCND1 and EGFR. *PloS one*, 8(10), e77299. <https://doi.org/10.1371/journal.pone.0077299>
- ⁷Morrison, C., Weterings, E., Mahadevan, D., Sanan, A., Weinand, M., & Stea, B. (2021). Expression Levels of RAD51 Inversely Correlate with Survival of Glioblastoma Patients. *Cancers*, 13(21), 5358. <https://doi.org/10.3390/cancers13215358>
- ⁸Würth, R., Patarozzi, A., Gatti, M., Bajetto, A., Corsaro, A., Parodi, A., Sironi, R., Massolino, M., Marini, C., Zona, G., Fenoglio, D., Sambuceti, G., Filaci, G., Daga, A., Barbieri, F., & Florio, T. (2013). Metformin selectively affects human glioblastoma tumor-initiating cell viability: A role for metformin-induced inhibition of Akt. *Cell cycle (Georgetown, Tex.)*, 12(1), 145–156. <https://doi.org/10.4161/cc.23050>
- ⁹Blyufer, A., Lhamo, S., Tariq, I., Thavornwatanayong, T., & Mahajan, S. S. (2021). Riluzole: A neuroprotective drug with potential as a novel anti-cancer agent (Review). *International journal of oncology*, 59(5), 95. <https://doi.org/10.3892/ijo.2021.5275>
- ¹⁰Ebrahim, T., Abasi, M., Seifar, F., Eyyazi, S., Hejazi, M. S., Tahrizi, V., & Montazersahab, S. (2021). Transplantation of Stem Cells as a Potential Therapeutic Strategy in Neurodegenerative Disorders. *Current stem cell research & therapy*, 16(2), 133–144. <https://doi.org/10.2174/1574888X15666200628141314>
- ¹¹A study to assess the pharmacodynamics of VK0214 in male subjects with amn - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved July 21, 2022, from <https://clinicaltrials.gov/ct2/show/NCT04973657>