

Guidance Cue

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NF Hackathon 2

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Project Goal: To explore the role of slit/robo pathway in the neurofibroma samples.

Method:

- 1. Used pre-developed tools (GSVA) in Bioconductor to discover normalized expression levels of guidance cue markers in all the samples available.
- 2. Visualized the slit/robo pathways in all the the samples.
- 3. Correlate significance of slit/robo pathways with the rest of the pathways.

Slit/Robo

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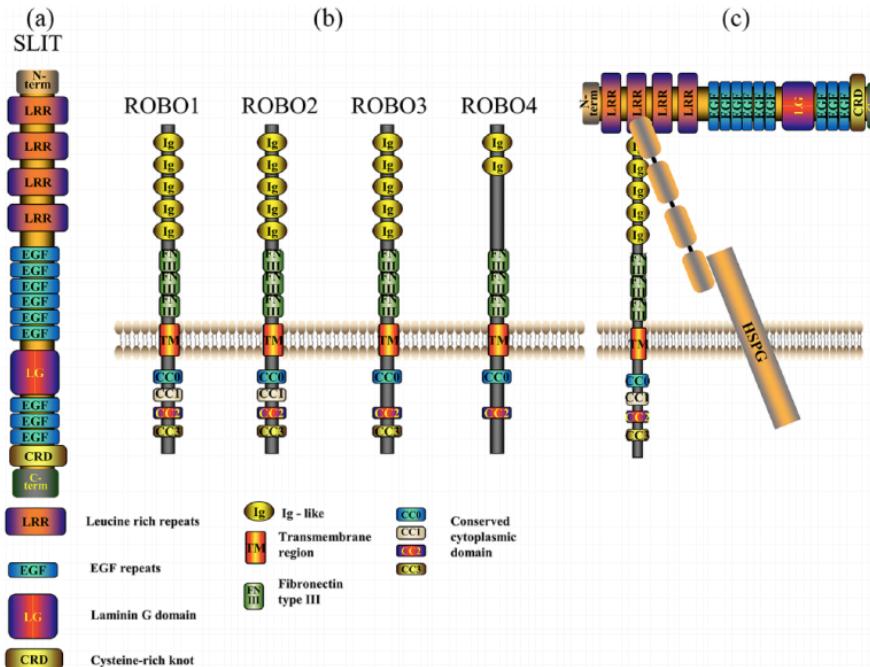
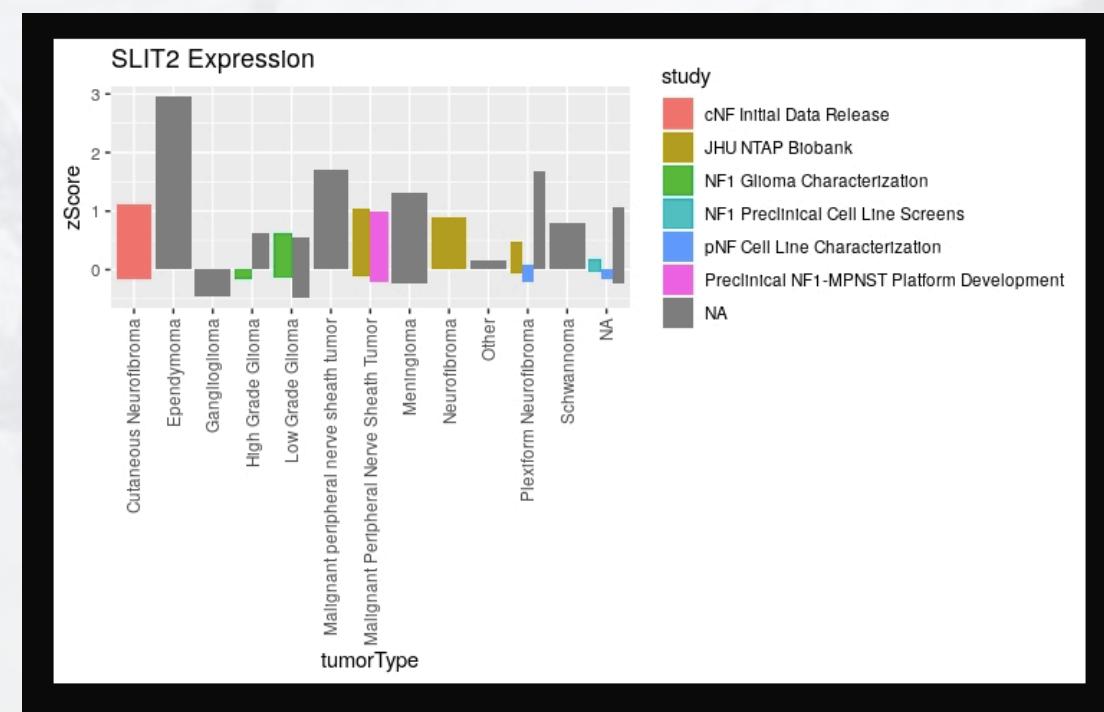
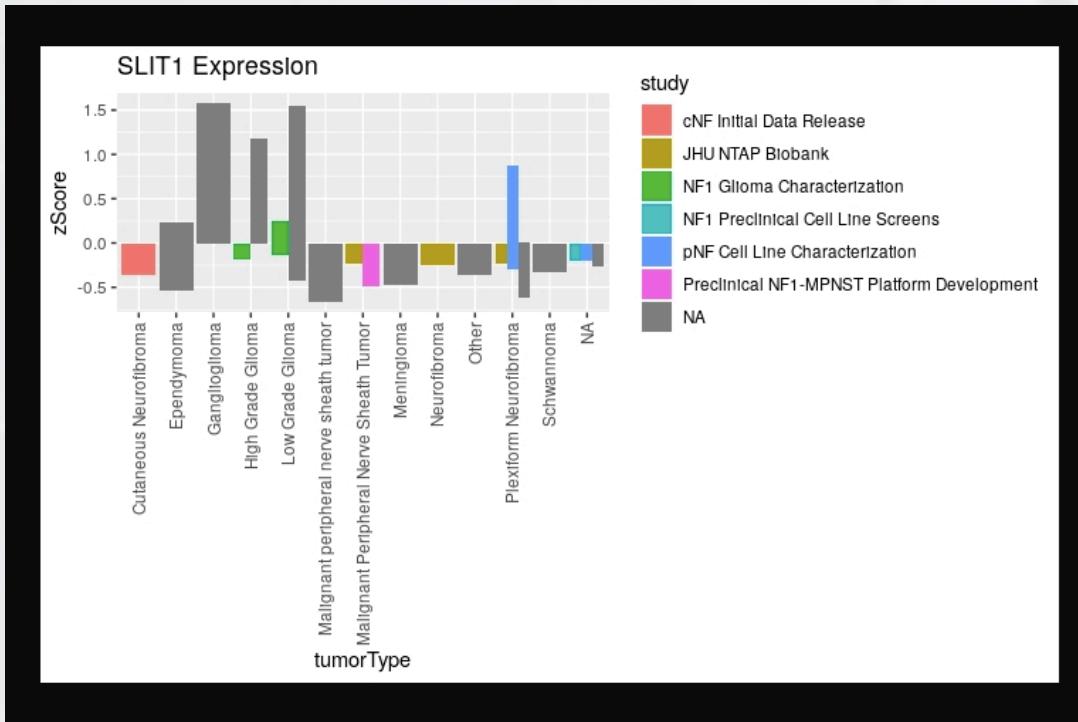
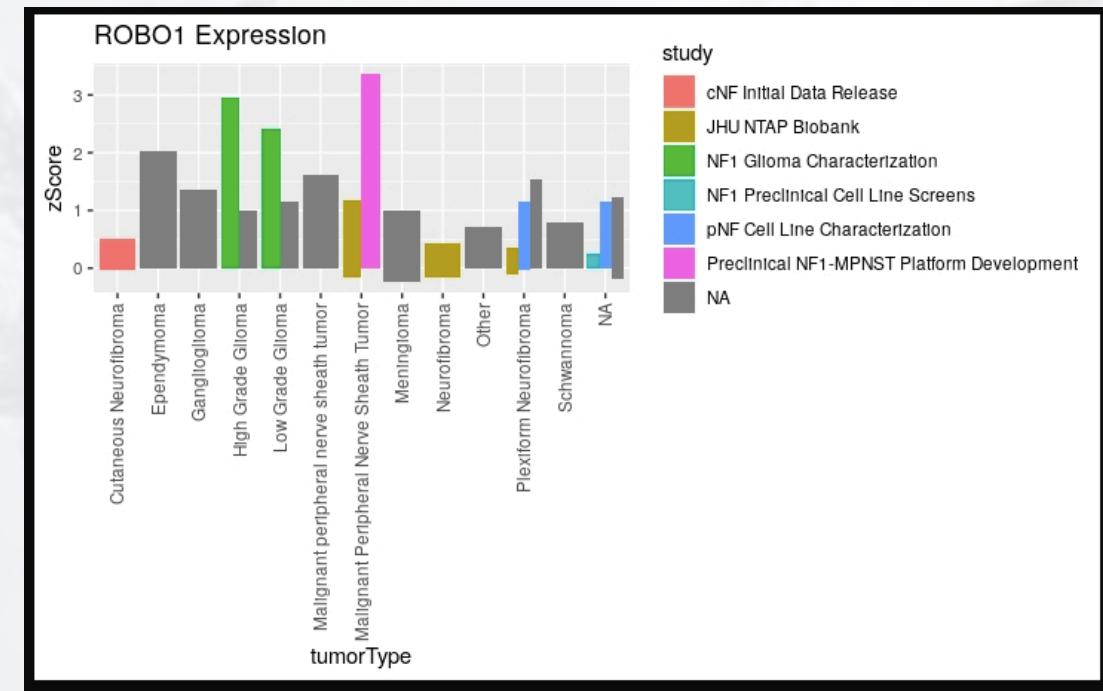
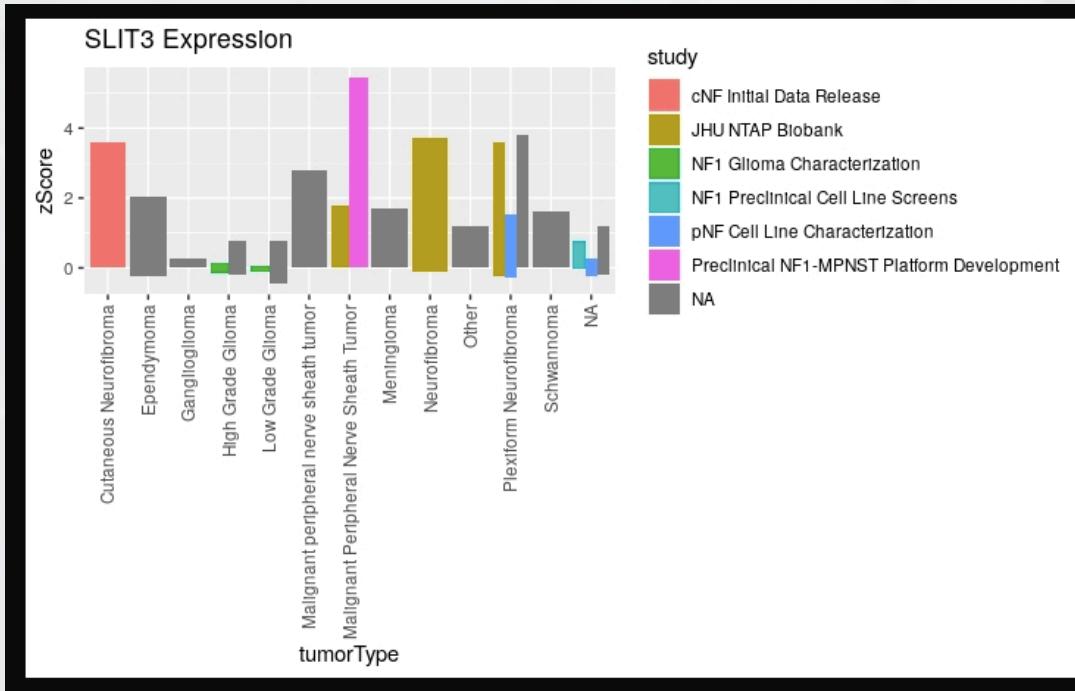


Figure 1. Structure of the SLIT/ROBO protein family. (a) Structure of SLIT protein, a secreted glycoprotein from the N terminus to C terminus, contains four leucine-rich repeats [LRRs, D1-D4], seven to nine epidermal growth factor [EGF] repeats, a laminin G-like module and a cysteine-rich knot. (b) The ROBO family contain five immunoglobulin [Ig] domains, three fibronectin type III modules in the extracellular region, one transmembrane region and one intracellular conserved cytoplasmic domain including CC0, CC1, CC2, and CC3. (c) SLIT D2 binds on its concave surface to the Ig1 domain of ROBO through electrostatic and hydrophobic contact regions such as the heparan sulfate proteoglycan [HSPG] syndecan.

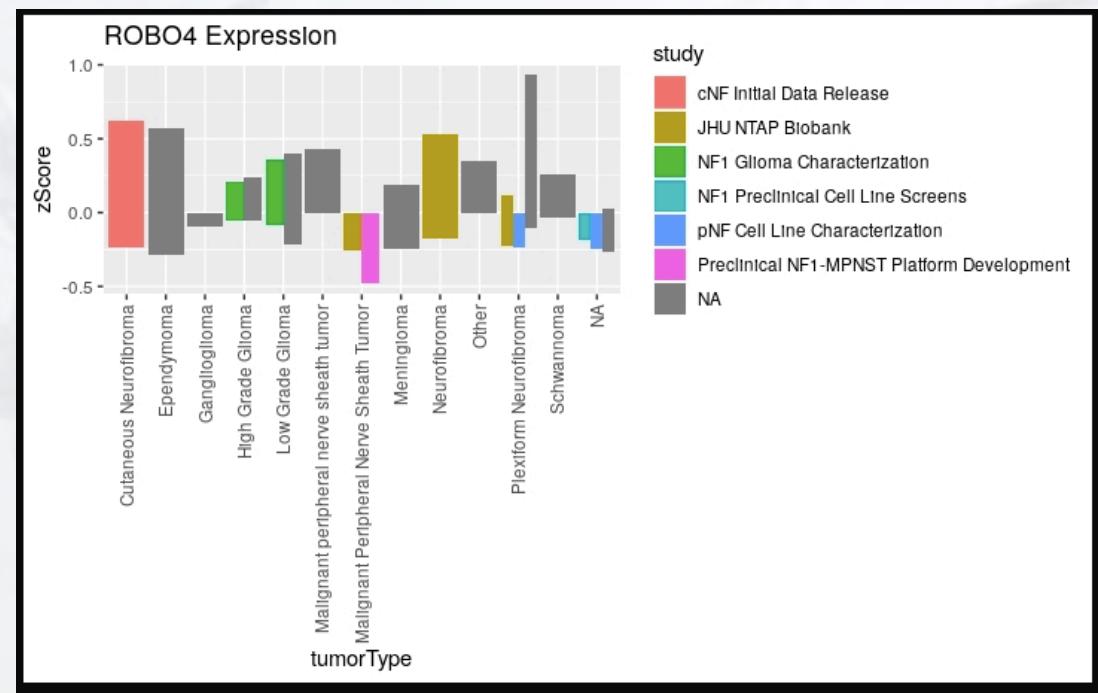
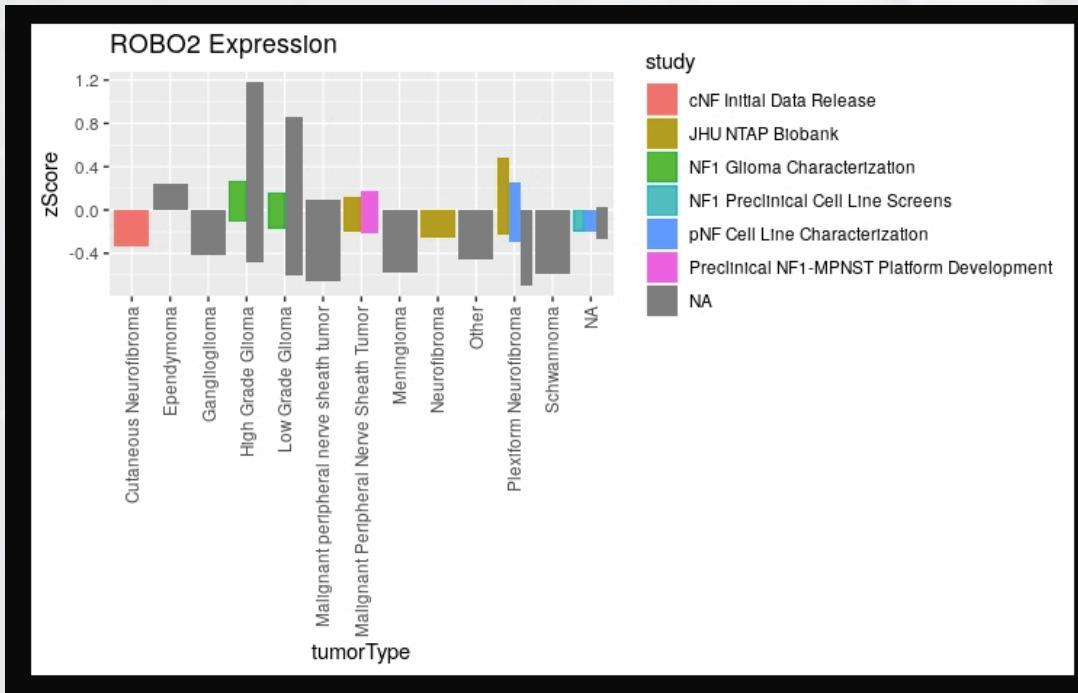
Normalized Expression Level



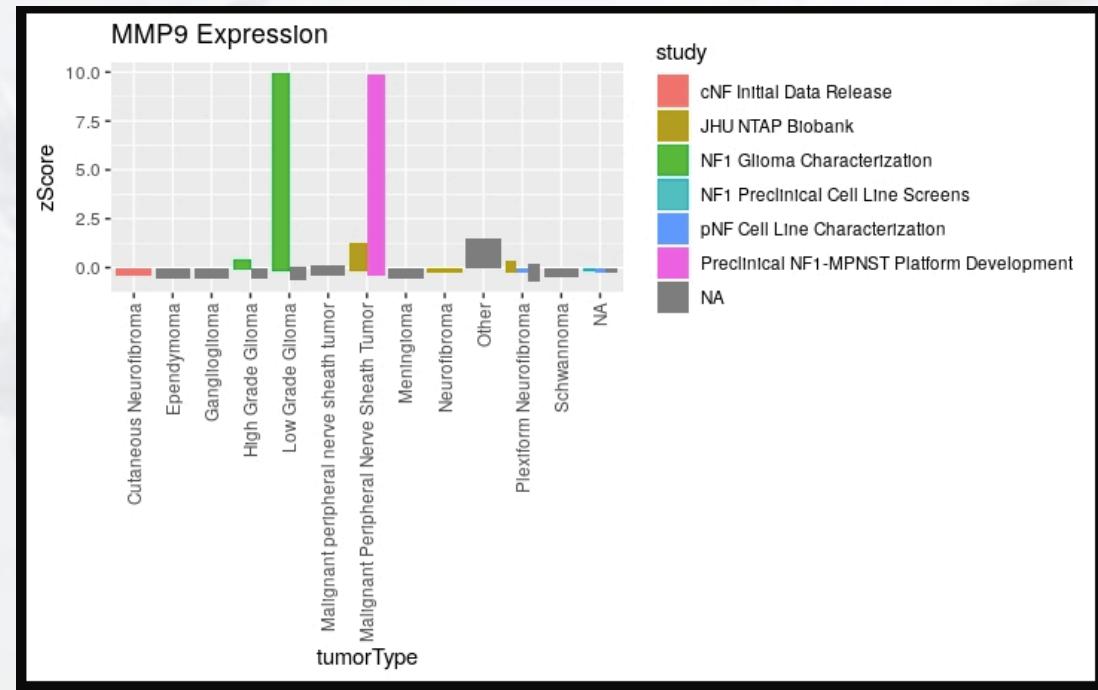
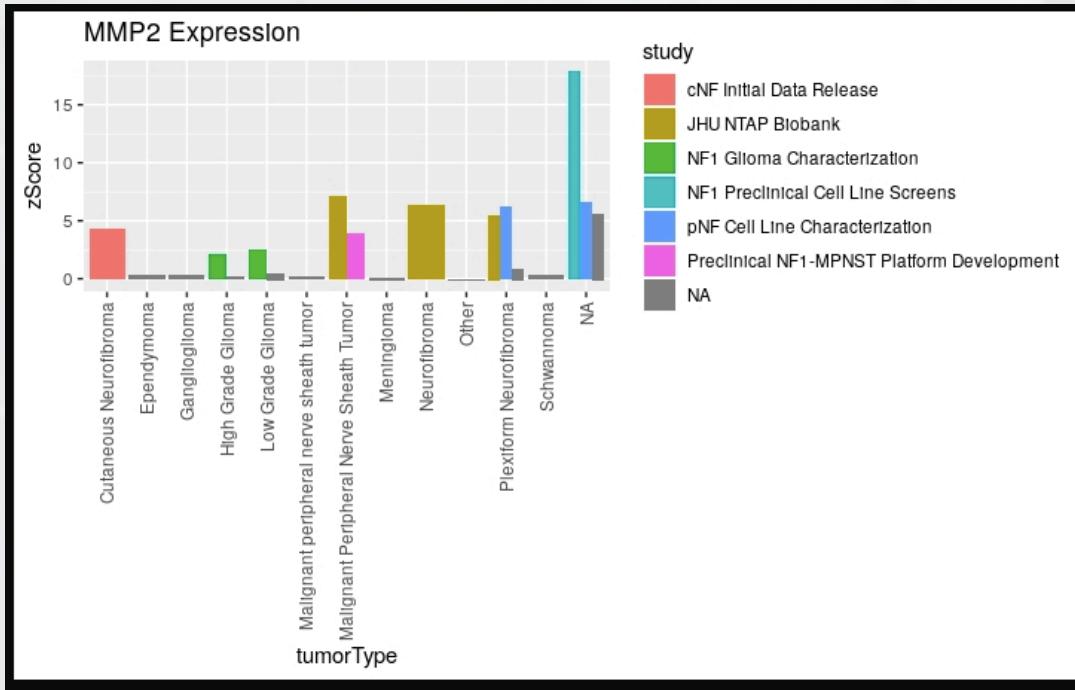
Normalized Expression Level



Normalized Expression Level



Normalized Expression Level



Slit/Robo Pathway

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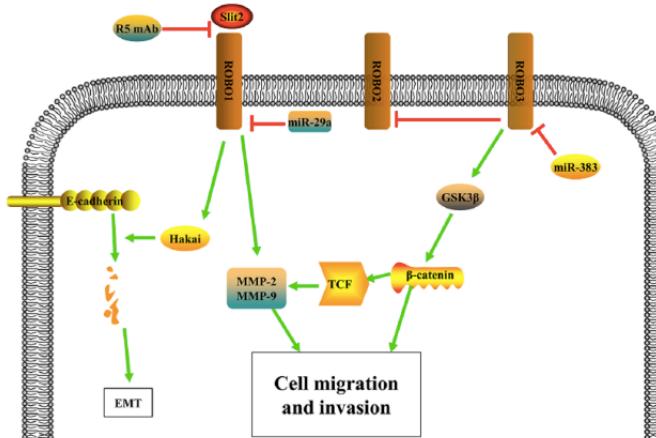


Figure 2. Mechanisms of the SLIT/ROBO pathway as an oncogene in cancer. The SLIT2/ROBO1 signal upregulates MMP-2 and MMP-9, thus promotes cell migration and invasion. SLIT2/ROBO1 signal recruits a ubiquitin ligase Hakai for E-cadherin ubiquitination and lysosomal degradation and thus promotes the epithelial-mesenchymal transition (EMT). The monoclonal antibody R5, which can interrupt the SLIT2/ROBO1 pathway, causes significantly suppressed cell growth and proliferation. ROBO3 promotes cancer cell growth, invasion and metastasis, which is associated with activated Wnt pathway components, β -catenin and GSK-3 β , and other markers indicating the EMT, and miR-383 functions as a suppressor of ROBO3.

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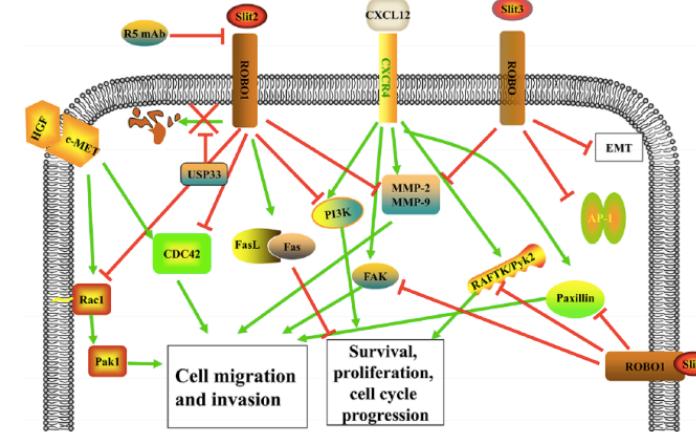
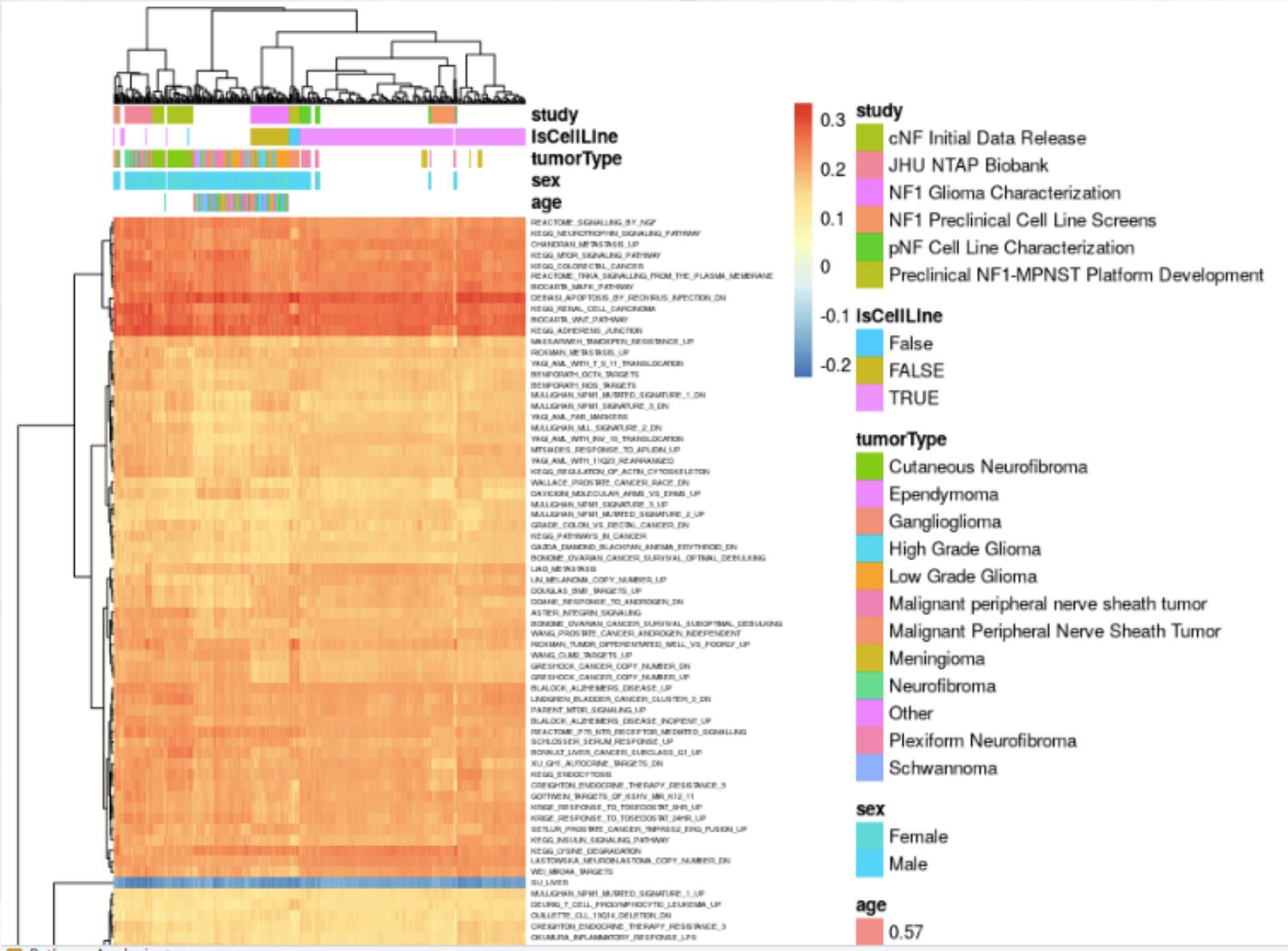
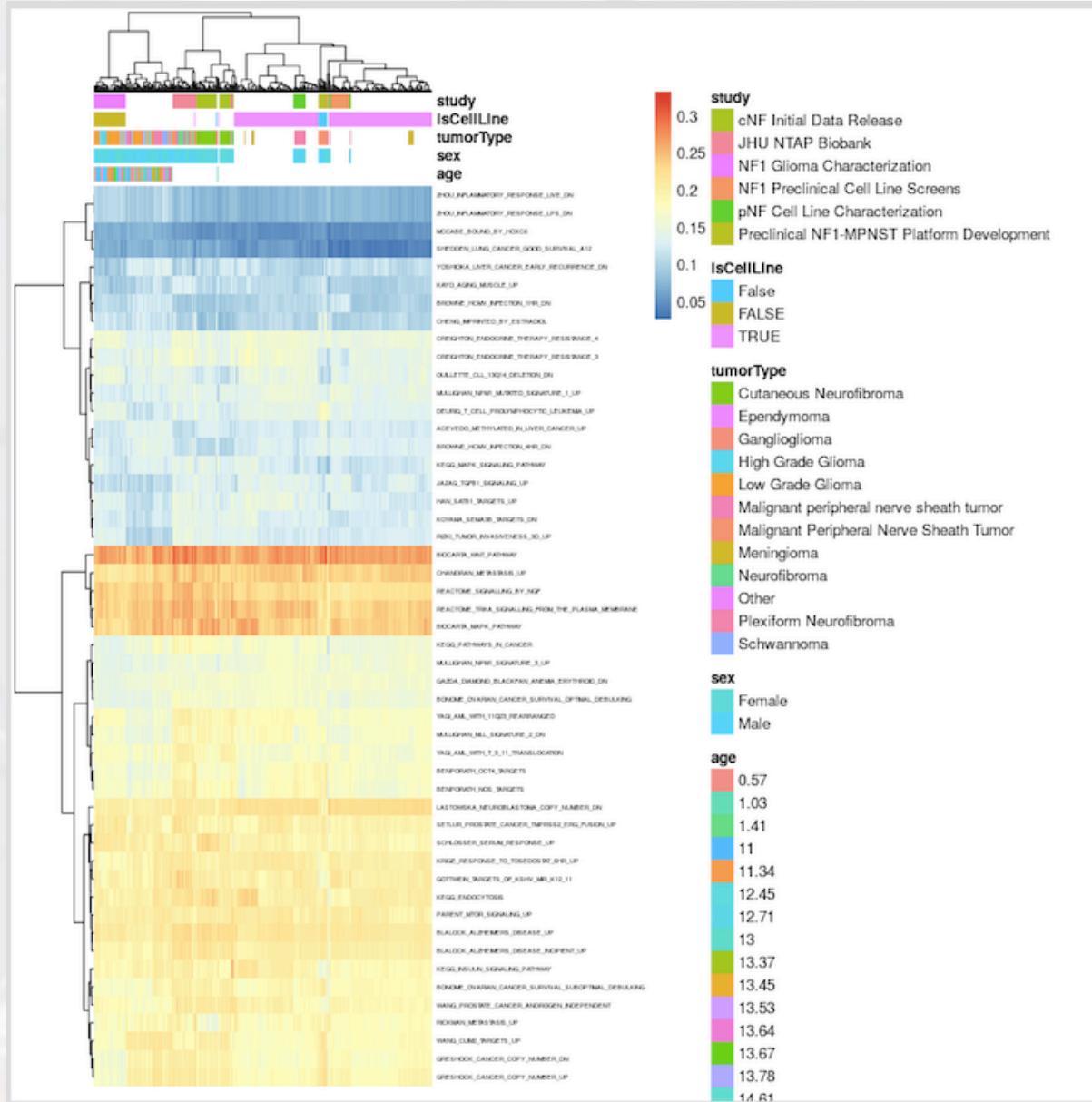


Figure 3. Mechanisms of the SLIT/ROBO pathway as a tumor-suppressor gene in tumor progression. SLIT2/ROBO1 signal decreases the proliferative rate and increases the apoptotic rate through regulating Fas-FasL proteins and PI3K/AKT pathway. USP33 can inhibit the lysosomal degradation of ROBO1, and SLIT3 leads to strong inhibition of migration through downregulation of AP-1 activity and targeting vimentin, MMP2, and MMP9. SLIT2/ROBO1 signal prevents hepatocyte growth factor (HGF)-induced motile responses, reduces Cdc-42 activation, and stimulates Rac-1 activities and, thus, inhibits cell proliferation, survival, and motility. SLIT2/ROBO1 functions as negative regulators of CXCL12/CXCR4 pathway through inhibiting CXCL12-induced tyrosine phosphorylation of focal adhesion components such as RAFTK/Pyk2, FAK, and Paxillin.





Conclusion

- Move over merlin, we may have a new role player in town!
- What is the role of slit/robo pathway in the neurofibromas?

Reference

- <https://journals.sagepub.com/doi/pdf/10.1177/1758835919855238>
- Oster SF¹, Deiner M, Birgbauer E, Sretavan DW. **Ganglion cell axon pathfinding in the retina and optic nerve.** Semin Cell Dev Biol. 2004 Feb;15(1):125-36.