

Predicting candidate small molecules for neurofibromatosis type 1 using a disease signature reversion-based approach

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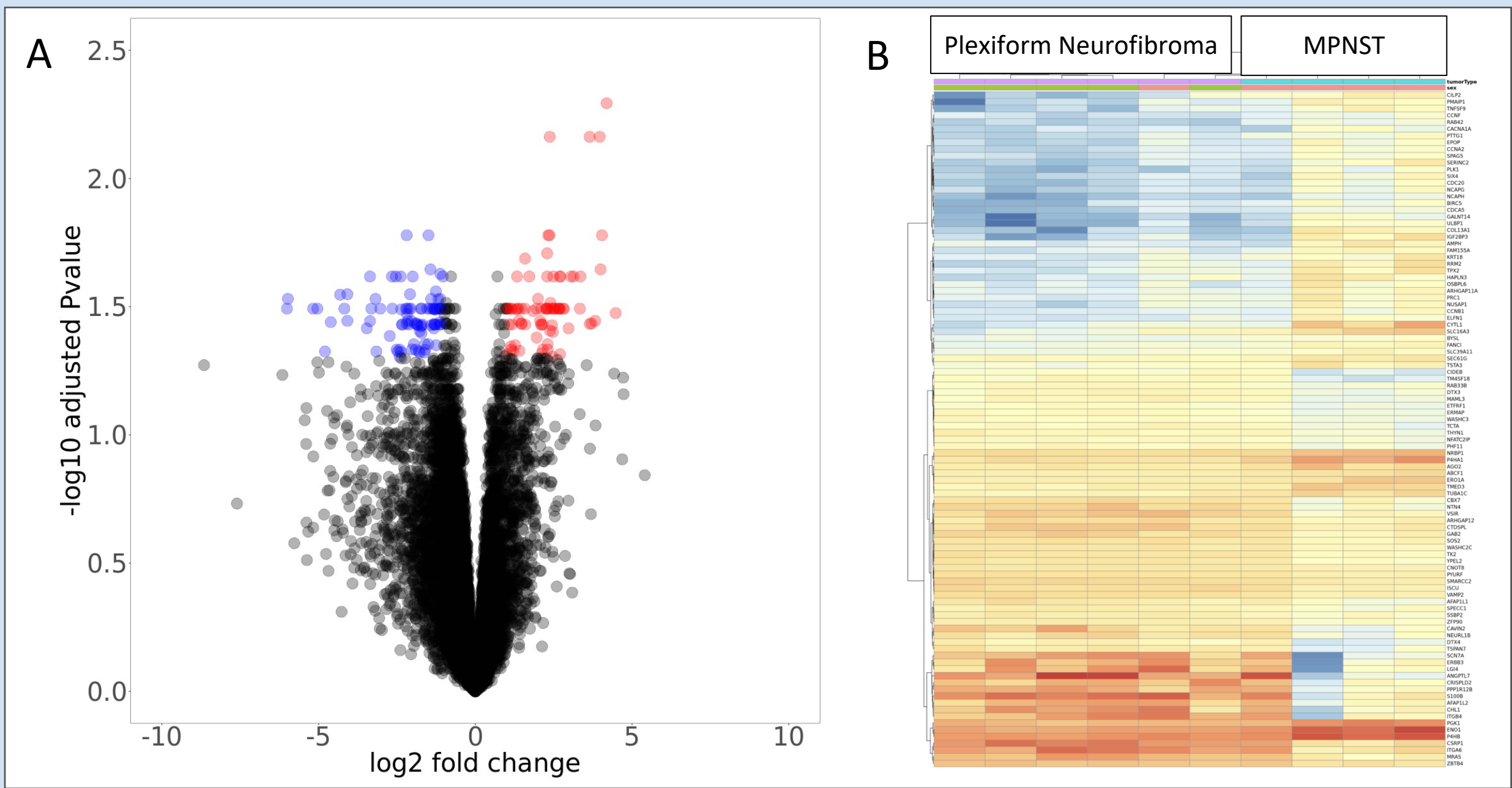
Highlights

- Very few therapeutic strategies exist for malignant peripheral nerve sheath tumors (MPNST) and plexiform neurofibromas (pNF) with the recent exception of Koselugo (selumetinib) for pNF ^{1,2}
- pNFs sometimes undergo malignant transitions to MPNSTs, potentially triggered by changes in gene expression
- We applied a new pattern recognition-based method called DRUID (DRUG Indication Discoverer)³ on publicly available gene expression data from human tumor samples banked at the Johns Hopkins NF1 Biospecimen Repository (JHU Biobank)⁴
- We identified candidate small molecules which could potentially reverse the changes in gene expression identified between these two tumor types.

Introduction

- Neurofibromatosis affects approximately 1 in 3500 people, making it the most common rare disease⁵. Manifestations of tumors in patients are highly heterogeneous and some tumor-types like benign pNFs can progress into MPNSTs with poor prognosis⁶
- DRUID (DRUG Indication Discoverer) is a pattern recognition-based approach to identify profiles of small molecules and compounds that may revert a condition of interest (in our case MPNST)³.
- We used DRUID to prioritize candidate compounds selected from databases like CMAP, LINCS, Small molecules, Natural products, and Comparative Toxicogenomic Database, that could potentially reverse the expression profiles that were significantly changed between MPNST and pNF.

Differentially expressed genes in human MPNST and pNF tumors



We applied EdgeR-limma statistical packages on normalized gene expression profiles of human MPNST and pNF tumor tissue to generate a list of differentially expressed genes (DEG).

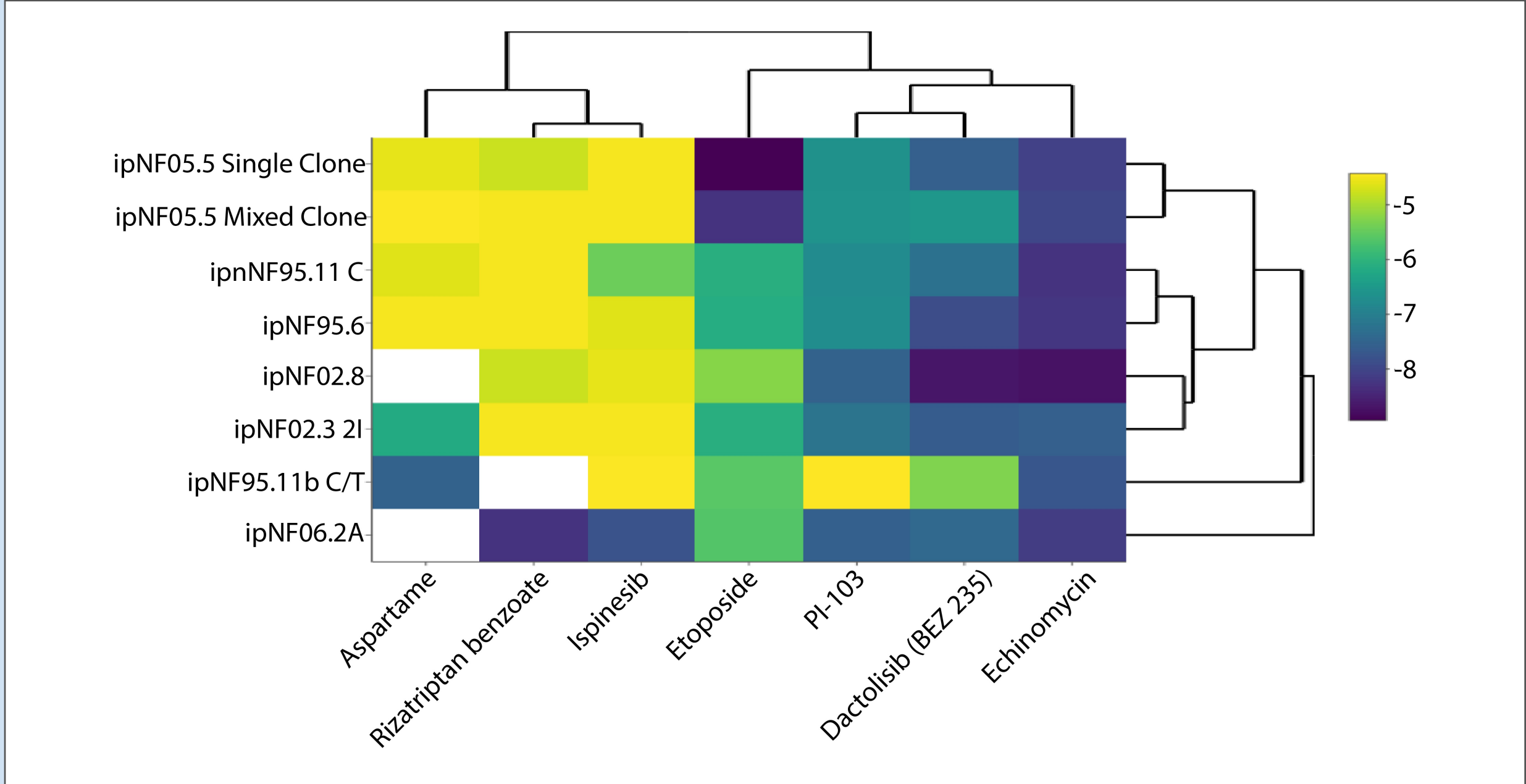
- A. Volcano plot showing differentially expressed genes in the human MPNST and pNF tumor samples. The red and blue dots represent some of the significantly upregulated or downregulated genes respectively.
- B. Heatmap showing the expression levels of top 100 differentially expressed genes in human MPNST and pNF tumor samples

Top 10 small molecules predicted using medium and high expression genes

Rank	Drug Name	DRUID score	Probability_random	Cell Line
1	Etoposide	6	0	MCF7
2	Rizatriptan	6	0	A549
3	Japonicone A	6	0.0001	MCF7
4	NSC-95937	5.94	0	HA1E
5	Monobenzone	5.91	0	MCF7
6	ZSTK-474	5.86	0	ASC
7	Ispinesib	5.84	0.0001	SKB
8	NVP-BEZ235	5.83	0	HEPG2
9	NVP-TAE684	5.80	0.0001	HA1E
10	PI-103	5.79	0.0001	A549

- Table of top 10 candidate small molecules predicted by DRUID
- High DRUID score (6) suggests that a compound's signature is similar to the DEG signature of MPNST and pNF, taking into account that the probability of achieving this similarity is significantly greater than random.
- The 'Cell Line' column suggests the name of the cell line on which a compound was tested and the resulting gene expression profile was stored in the database queried by DRUID

Many of the top 10 candidates show low toxicity to pNF cell lines



- The heatmap shows log₁₀AC50 (half maximal activity) measures for select candidates from the top 10 list of predicted compounds. Aspartame and Echinomycin have been added as examples of compounds with low (yellow) and high effect (blue) on pNF cell lines respectively.
- Drug screening results of selected compounds in pNF cell lines (derived from publicly available data) show relatively low toxicity to pNF cells⁷.
- Our future directions include validating these compounds on MPNST cell lines.

Discussion and Future Directions

- We generated a list of genes whose expression is significantly altered in human pNF and MPNST tumor samples
- We applied DRUID to identify candidate compounds predicted to revert the MPNST gene expression profile and used publicly available data to show that the predicted compounds have low toxicity towards pNF cell lines.
- Future work includes collaborating with drug screening labs and testing these compounds on MPNST cell lines to validate whether they can successfully reduce the viability of MPNST cells or change gene expression profiles when applied to the malignant cell lines.

Data Acknowledgement and References

- Data Contributors: [JHU Biobank](#), NCATS, [NF Data Portal](#) (The results published here are in whole or in part based on data obtained from the NF Data Portal and made available through the NF Open Science Initiative.)
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NTAP

NF DATA PORTAL