Integrated genomic and epigenetic analyses reveal distinct regulatory pathways in NF2-associated and sporadic vestibular schwannomas

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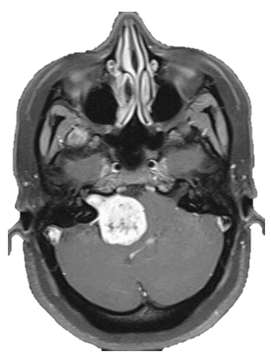
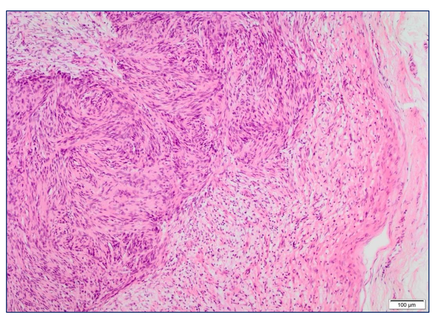
Background

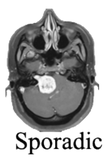
- Vestibular schwannomas (VS) are benign tumors of the vestibulocochlear nerve that arise either sporadically or in association with neurofibromatosis type 2 (NF2) syndrome.
- NF2-associated tumors follow a more aggressive clinical course
- Defining the epigenetic and transcriptional differences between sporadic and NF2-associated VS may clarify mechanisms of treatment resistance and reveal potential therapeutic targets.





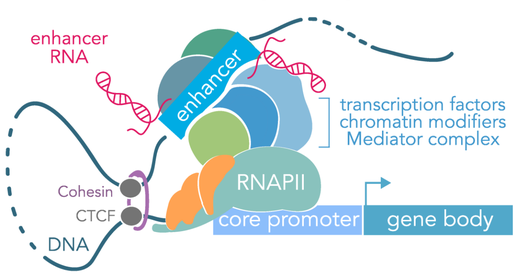
Methods

- 32 VS tumors were profiled using DNA methylation, bulk RNA sequencing, and single-nucleus RNA/ATAC sequencing



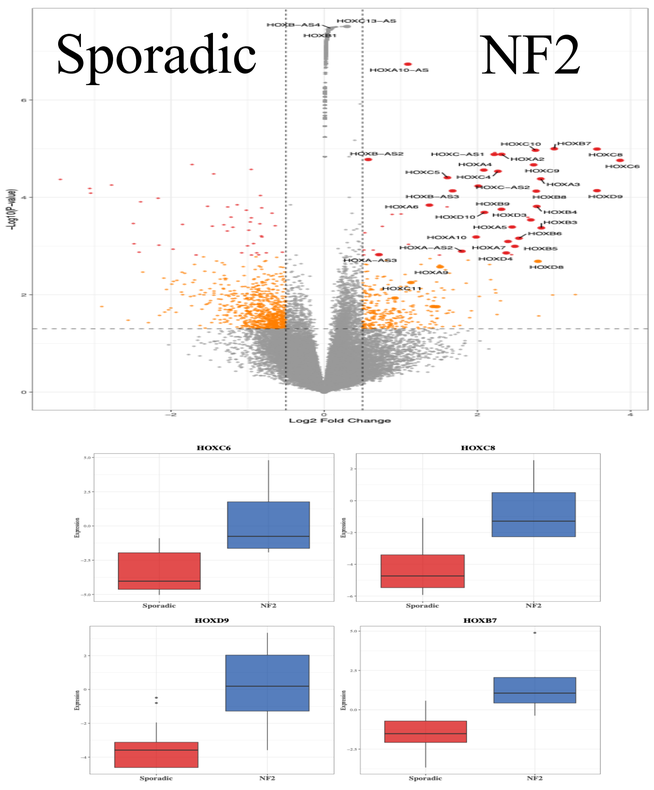
	RNA-seq	DNA methylation	snRNA-seq and snATAC-seq
Sporadic	16 samples	16 samples	9,016 cells from 4 patients
NF2	16 samples	16 samples	11,491 cells from 6 patients

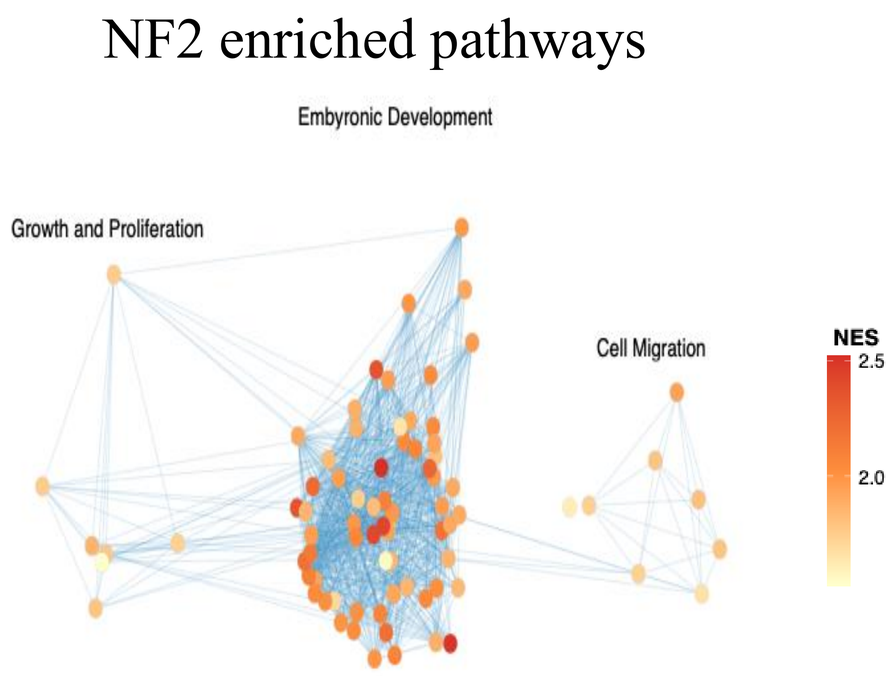
- Gene regulatory networks were reconstructed by integrating chromatin accessibility with gene expression to define enhancer-driven transcriptional programs.



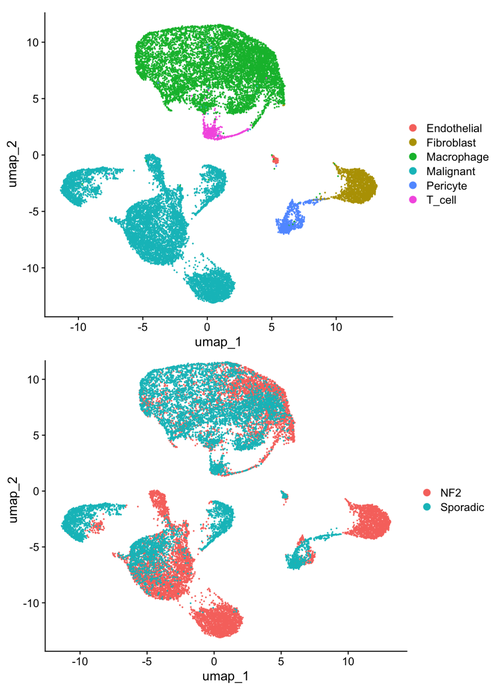
Results

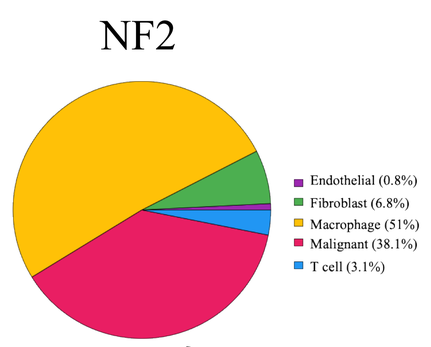
HOX family genes expression is upregulated in NF2-associated VS

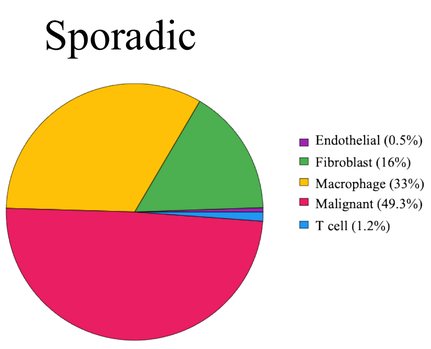


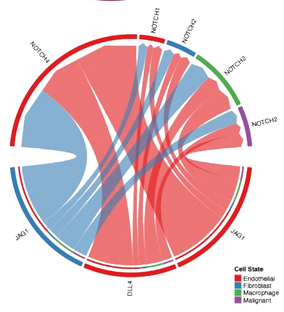


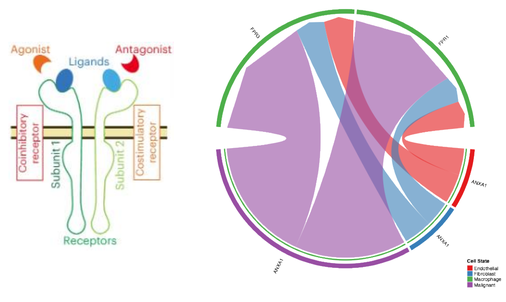
Single cell atlas of NF2 and sporadic VS reveal divergent microenvironment and signalling pathways



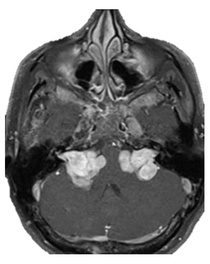


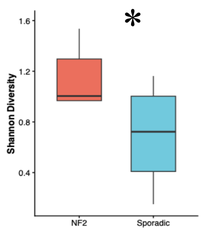


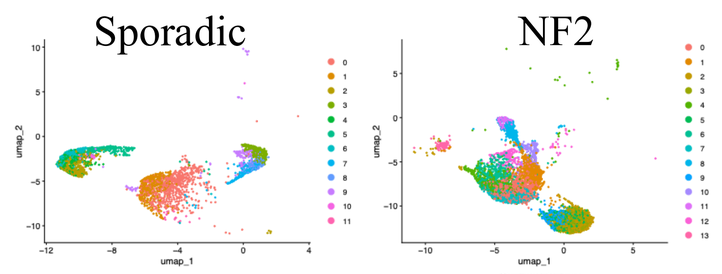


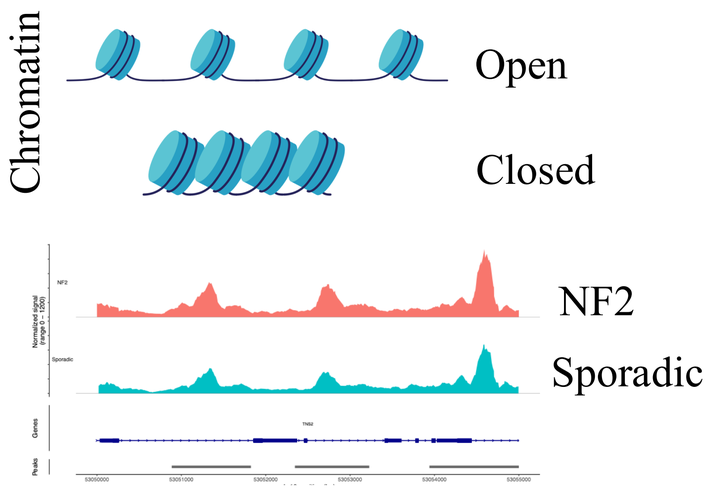


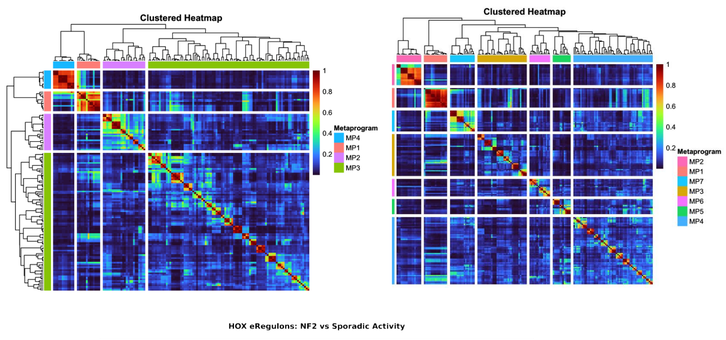
NF2-associated VS have increased neoplastic cell heterogeneity and regulatory networks

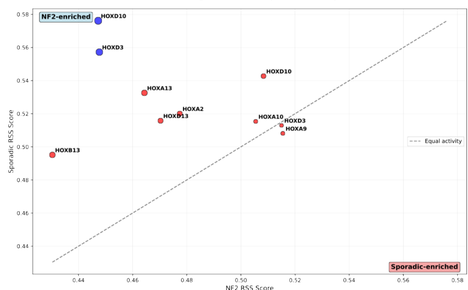












Chromatin accessibility

Conclusions

- HOX genes serves as enhancer-driven regulators of NF2-VS but not sporadic.
- NF2 VS have a unique tumor microenvironment with increased fibroblasts and NOTCH signalling.
- NF2 VS malignant cells have increased transcriptional heterogeneity.
- Sporadic VS have increased inflammatory signalling pathways.