Comparative Molecular and Tumour Microenvironment Profiles of Sporadic & NF2-Related Schwannomatosis Vestibular Schwannomas: A Systematic Review

Gabriel Berberi, BSc[1]; Lea Stephan[1]; Marie Kametani, BSc[2]; Jo Anne Stratton, PhD[2]; Emily Kay-Rivest, MD, FRCSC[3]

1. Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada; 2. Department of Neurology and Neurosurgery, McGill University, Montreal, Canada; 3. Department of Otolaryngology-Head and Neck Surgery, McGill University, Montreal, Canada

INTRODUCTION

- Vestibular Schwannomas (VS) are **benign neoplasms** that arise from **Schwann cells** of the vestibulocochlear nerve (CN-VIII).
- Two types of VS: sporadic VS (sVS) & NF2-related schwannomatosis VS (NF2-VS)
- Studies have shown **overlapping** and **diverging molecular and tumor microenvironmental (TME) features** between sVS and NF2-VS.
- Currently, no systemic reviews have explored the TME in sVS and NF2-VS.

OBJECTIVE

- Determine the molecular and tumor microenvironmental (TME) similarities and differences between sVS and NF2-VS.

METHODS

- **Search strategy:** MEDLINE, Embase, Web Of Science, and Scopus
- **Inclusion criteria:** Original articles including individuals of any age or sex with VS exploring the molecular or TME features of VS.
- **Exclusion criteria:** Original articles where the VS subtype (sVS or NF2-VS) is not specified. Articles only reporting on animal or in-vitro VS models. Case reports, case series with n<10, or conference abstracts or proceedings.
- **Primary outcome:** Comparison of molecular or TME features between sVS, NF2-VS, or controls.
- **Secondary outcome:** Comparison of molecular or TME features across state-specific subgroups of sVS and/or NF2-VS.
- **Quality Assessment:** JBI critical appraisal tool for systematic reviews.

RESULTS

- We identified 66 studies, reporting on 4,289 patients with 4,305 unique VS.

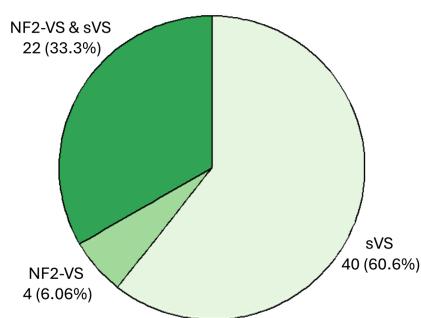**Figure 1. Pie Chart of Included Studies by VS Subtype Explored**

NF2-VS & sVS 22 (33.3%)
sVS 40 (60.6%)
NF2-VS 4 (6.06%)

Figure 2. Pie Chart of Included Studies by Study Design

Case-Series 3 (4.5%)
Case-Control 2 (3.0%)
Prospective Cohort 3 (4.5%)
Retrospective Cohort 8 (12.1%)
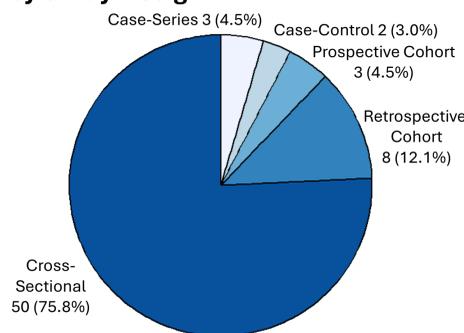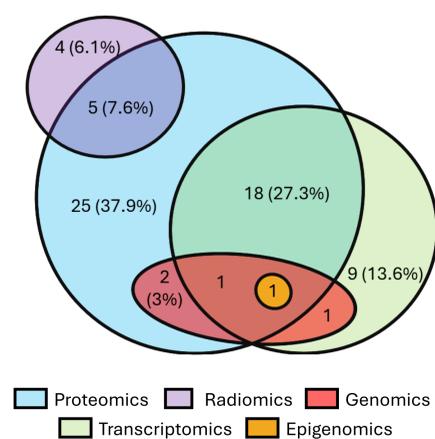Cross-Sectional 50 (75.8%)

Table 1. Summary of Patient Characteristics from all Studies

Patient Characteristics	Total (n = 4,289)
Patients with x1 VS sample	4,273 (99.62%)
Patients with x2 VS samples	16 (0.38%)
Unique VS Samples	4,305
sVS samples	3,792 (88.08%)
NF2-VS samples	513 (11.91%)
Age	
Mean Age (n = 3481)	47.45
Age Range	7-86
Sex	
Male	1,859 (43.35%)
Female	1,949 (45.44%)
Unspecified	481 (11.21%)

Figure 3. Venn Diagram of Explored Domains Across all Studies

4 (6.1%)
5 (7.6%)
25 (37.9%)
18 (27.3%)
9 (13.6%)
2 (3%)
1
1
1
1

Proteomics | Radiomics | Genomics | Transcriptomics | Epigenomics

Overall, 20 laboratory technique groups were identified, spanning 5 investigation domains (genomics, epigenomics, transcriptomics, proteomics, and radiomics).

sVS & NF2-VS comparison
- The TME in sVS and NF2-VS is **dominated by macrophages**, with complex interactions occurring between tumor cells and immune cellular components (Figure 4).
- Overall, the **TME is largely comparable**, with **only minor differences** between both VS subtypes. Out of 22 studies including sVS and NF2-VS, only 10 reported some differences in molecular or TME features. (Data not shown)

sVS & NF2-VS state-specific subgroup comparison
- VS subgroups based on **state-specific features** such as hearing status, irradiation status, size, growth, facial nerve function, or histoarchitecture **reveal more distinctions than sVS & NF2-VS subtype comparisons.** (Data not shown)

CONCLUSION

- Both sVS and NF2-VS **share core oncogenic and angiogenic programs**, along with a **comparable macrophage-predominant TME.**
- Subtype-specific differences exist but **were not always consistent** across studies, warranting further investigation.
- **State-specific comparisons (hearing status, irradiation, size, growth)** within VS-subtype revealed **more distinctions than subtype comparisons.**
- Future studies should focus on deeper molecular profiling and using modelling systems to clarify defined mechanisms critical for targeted interventions.

Figure 4. Schematic Representation of the Tumor Microenvironment in Vestibular Schwannomas

Legend:
- Schwannoma Tumor Cells
- Macrophages (Mφ) - M2φ: Alternative; M1φ: Classic
- Fibroblasts
- Endothelial Cells
- Pericytes
- T-cells - CD4+: Helper; CD8+: Cytotoxic
- B-cells
- Neutrophils (Nφ)
- Cytokines & soluble factors
- Extracellular Matrix & Collagen

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