

# Radiogenomics in NF2-Associated Schwannomatosis (Neurofibromatosis Type II): Exploratory Data Analysis

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**Abstract.** Our pilot study aimed at exploratory radiogenomic data analysis in patients with NF2-associated schwannomatosis (formerly neurofibromatosis type II) to assume the potential of image biomarkers in this pathology. Fifty-three unrelated patients (37 (69.8%) women, avg. age  $30.2 \pm 11.2$  y.o.) were enrolled in the study. First-order, gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), and geometry-based statistics were calculated (3718 features per region of interest). We demonstrated imaging patterns and statistically significant differences in radiomic features potentially related to the genotype and clinical phenotype of the disease. However, the clinical utility of these patterns should be further evaluated. *The study was supported by the Russian Science Foundation grant 21-15-00262.*

**Keywords.** Neurofibromatosis type II, NF2-associated schwannomatosis, genetics, mutations, radiomics, radiogenomics

## 1. Introduction

Radiogenomics can potentially expand the diagnostic toolkit in neurooncology, providing extra informative feature space to clinicians and augmenting qualitative image assessment [1]. This may be especially important for orphan genetic diseases, which include neurofibromatosis - a neurocutaneous syndrome, characterized by multiple tumors in the central and peripheral nervous system. According to the modern knowledge of the disease's genetic nature, neurofibromatosis type I is distinguished from a group of schwannomatosis, including that associated with the NF2 gene (formerly known as neurofibromatosis type II) [2]. Only a few works on radiomics and radiogenomics in neurofibromatosis type I can be found in the literature, while currently, there are no studies on radiomics in schwannomatosis.

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Our pilot study aimed at exploratory radiogenomic data analysis in patients with NF2-associated schwannomatosis. We hypothesized the existence of image biomarkers pointing at the genetic and clinical disease phenotypes.

## 2. Methods

Patients with NF2-associated schwannomatosis genetically full-tested for pathogenic NF2 mutation, having two-sided intracranial tumors (vestibular schwannomas) indicated for stereotaxic radiotherapy, were eligible for our research. All patients were examined at N.N. Burdenko Neurosurgery Center (Moscow, Russian Federation) to meet the updated clinical and molecular criteria for schwannomatosis suggested by S. Plotkin and G. Evans (2022) [2]. Genomic DNA was isolated from peripheral white blood cells using a standard protocol. To identify single nucleotide variants (SNVs) and short indels in the NF2 gene, targeted high-throughput sequencing was performed using Ion AmpliSeq amplification technology, AmpliSeq custom primer panel, and Ion Torrent GeneStudio S5 sequencer (Thermo Fisher Scientific, United States). The bioinformatic workflow for sequencing data analysis was produced on Torrent Suite software (version 5.12). All SNVs identified were verified via Sanger sequencing. We used multiple ligation-dependent probe amplification kit SALSA MLPA Probemix P044 to detect copy-number variations (CNVs). The pathogenicity of a variant was determined using the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines.

The magnetic resonance imaging (MRI) data obtained before irradiation were utilized for radiomic feature extraction. Topometric scans (T1, T1 contrast-enhanced, T2 and T2 FLAIR modalities) with thin slices (1 mm for T1 and T1 with contrast, 2 mm for T2 and T2 FLAIR) were used to segment the intracranial schwannomas in several variations. Rarely were scans obtained in the standard mode (5 mm thick). The majority of images were presented in the axial projection. Schwannomas that had not undergone radiation treatment previously were contoured section-wise in the iPlan software (BrainLab) for all MR modalities available.

Radiomics features extraction and analysis were performed using the R programming language (version 4.2.2) in the RStudio Server IDE (version 2022.07.0+548) on an NVIDIA DGX A100 supercomputer. Radiomic data were computed from an MRI 3D array in each modality inside every region of interest (ROI) variant using the *RIA* library [3]. The voxel values from ROIs were discretized into 128 bins. We calculated first-order, gray level co-occurrence matrix (*GLCM*), gray level run length matrix (*GLRLM*) and geometry-based statistics (the complete list of features is presented in [4]). We redesigned the original *GLCM* and *GLRLM* functions from the *RIA* package to accelerate the computation speed a thousandfold and reduce processing time.

We tested the relation of all the radiomic features extracted to the following molecular and clinical target variables, defining the diagnosis:

- 1) Categorical (binary): mutation impact on FERM-domain; mosaic/germinal mutation form; truncating/non-truncating mutation; the variants of the copy number (CNV) and single nucleotide polymorphisms (SNV); disease severity (the only general clinical target);
- 2) Numeric (ordinal): the number of the exon corrupted;
- 3) Numeric (continuous): allele frequency.

The differences in radiomic features between the levels of categorical target variables and correlations of radiomic features with numeric target variables were tested for statistical significance ( $p < 0.05$ ). The groups of potential predictors for target variables were evaluated for importance via the Boruta algorithm.

3. Results

Fifty-three unrelated patients (37 (69.8%) women, avg. age  $30.2 \pm 11.2$  y.o.) were enrolled in this pilot study. The most frequent SNV subtype was nonsense ( $n = 20$ ). Besides, 15 frameshift, four missense, and seven splice site variants were identified. CNV subtype was observed in 7 patients. Most cases were germline ( $n = 35$ ) variants. De novo variants were met in 51 cases (96,2%).

A standard set of 3718 radiomic features was calculated for every ROI in each MR modality. Table 1 shows the modalities that produced the most critical radiomic features in pairwise statistical tests (Best Diff. / Corr. Modality) and with Boruta (Best Pred. Modality). The number of features is shown correspondingly.

**Table 1.** The most significant modalities for the genotype and phenotype prediction with the corresponding number of potential predictors.

Target variable	Target type	Best Diff. / Corr. Modality	Best Pred. Modality (Boruta)	N Different Features ( $p < 0.05$ )	N Important predictors (Boruta)
Exon number	Numeric, ordinal	T1+C	T2, T1+C	775 - 1225	5 - 14
Allele frequency	Numeric, continuous,	T2 Flair, T1	T1+C, T2 Flair	636 - 970	5 - 9
Impact on FERM- domain	Categorical, binary	T1+C, T2 Flair	T2 Flair	476 - 559	2 - 10
Mosaic/Germinal	Categorical, binary	T1+C	T2, T1+C	312 - 364	3 - 22
Truncating mutation	Categorical, binary	T2 Flair, T2, T1+C	T2 Flair, T2	115 - 150	3 - 6
CNV/SNV	Categorical, binary	T2	T2	79-107	2 - 6
Disease severity	Categorical, binary	T2	T2	90 - 116	4 - 5

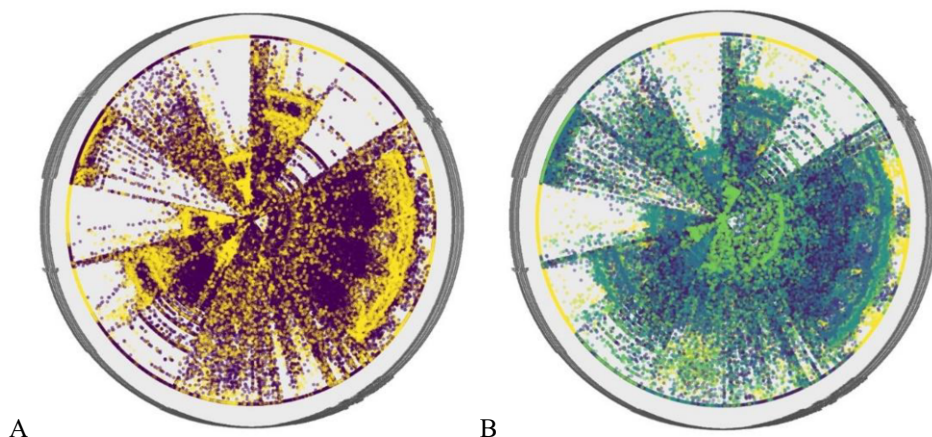
Figure 1 shows potential neuroimaging patterns for different genetic mutation variants. All radiomics parameters calculated in a given modality for a given ROI were scaled in the interval  $[0,1]$  and plotted in polar coordinates. The values of the target variables are shown in color. The uneven distribution of these values may indicate the presence of imaging patterns related to tumor genotype or clinical phenotype.

4. Discussion

The molecular and clinical diagnosis of schwannomatosis is complicated and expensive. Nearly 30% of mutations are mosaic variants that could be difficult to identify. Besides, CNV and SNV variants are pretty common.

The number of differential and predictive features shown in Table 1 suggests that genetic targets have a higher potential to be assumed by MRI rather than general clinical severity. Thus, the study reveals statistically supported radiomic patterns that could probably relate to genetics. That brings a fundamental hypothesis for future work.

The limitations of this study were the number of patients, heterogeneity in disease duration, imaging timing, setups, and formats. However, to the best of our knowledge, this is the first radiogenomic study in NF2-associated schwannomatosis. The next step would be to model the relationship between genetic, clinical, and radiomic features in various ways, preferably on a bigger sample size.



**Figure 1.** Examples of the visual radiomic patterns in polar coordinates (each axis is a radiomic feature). The intensity of target variables is distributed unevenly over the radiomic axes. A – T1+C modality; yellow codes germinal variant, dark inky is mosaic. B – T1+C modality; a lighter color codes a higher exon number.

## 5. Conclusion

The study revealed radiomics-based imaging patterns potentially related to the genotype and clinical phenotype of NF2-associated schwannomatosis. However, the clinical utility of these patterns is the subject of future assessment. *The study was supported by the Russian Science Foundation grant 21-15-00262.*

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