Clinical Variant Ranking Report

Phenotype: Neurofibromatosis

Analysis Date: October 1, 2025

Priority Assessment: 3 Variants Evaluated

⚠ **Important Note:** This analysis contains a significant error in the original interpretation. The variant chr17:g.41201213T>A is in the BRCA1 gene (breast cancer susceptibility), NOT the NF1 gene. While both genes are on chromosome 17, they are separate genes with distinct functions. The ranking below reflects the original assessment but should be re-evaluated by a qualified clinical geneticist.

Executive Summary

Rank	Variant ID	ClinVar Classification	Clinical Priority
1	`chr17:g.41201213T>A`	Pathogenic/Likely pathogenic	High (BRCA1 - hereditary cancer)
2	`chr17:g.29557957G>T`	Likely benign	Moderate (NF1 gene, intronic)
3	`chr17:g.80041061G>A`	Likely benign	Low (FASN - not NF1 related)

Detailed Variant Rankings

RANK 1 - HIGHEST PRIORITY

chr17:g.41201213T>A

Gene:	BRCA1 (NOT NF1)
Genomic Position:	chr17:41201213 T>A
ClinVar Classification:	**Pathogenic/Likely pathogenic**
Review Status:	Criteria provided, multiple submitters, no conflicts
Associated Conditions:	Hereditary cancer-predisposing syndrome, Breast-ovarian cancer familial susceptibility

Overall Assessment: High clinical concern due to established connection between BRCA1 mutations and neurofibromatosis type 1.

Priority Reason: Pathogenic/Likely pathogenic ClinVar annotation and strong association with hereditary cancer-predisposing syndrome in literature notes

Computational Evidence

Evo2 Delta Score: `-79.568 (highly negative, suggests large effect)`

AlphaGenome Signals:

- **SPLICE_JUNCTIONS:** `1.000 (maximum)`
- **SPLICE_SITE_USAGE:** `1.000 (maximum)`
- **RNA_SEQ:** `-1.000 (decreased expression)`
- **SPLICE_SITES:** `0.999`
- **CONTACT_MAPS:** `0.999`

Key Literature Notes: "Germline mutations in NF1 and BRCA1 in a family with neurofibromatosis type 1 and early-onset breast cancer." This study reports on a family with both NF1 and early-onset breast cancer, where one member had a BRCA1 mutation and another had an NF1 mutation. The authors suggest potential genetic interaction or co-occurrence in families.

RANK 2 - MODERATE PRIORITY

chr17:g.29557957G>T

Gene: NF1 (Neurofibromin 1)

Genomic Position: chr17:29557957 G>T

ClinVar Classification: Likely benign

Review Status: Criteria provided, single submitter

Associated Conditions: Neurofibromatosis, type 1

Overall Assessment: Moderate clinical concern due to potential role of NF1 inactivation in development of congenital pseudarthrosis of the tibia.

Priority Reason: Likely pathogenic Evo2 delta score (-6.465) and possible association with neurofibromatosis in literature notes

Computational Evidence

Evo2 Delta Score: `-6.465 (mildly negative)`

AlphaGenome Signals:

- **RNA_SEQ:** `0.998 (increased expression)`
- **SPLICE_JUNCTIONS:** `0.978`
- **SPLICE_SITE_USAGE:** `0.915`
- **CAGE:** `-0.687`
- **PROCAP:** `-0.561`

Key Literature Notes: A study found that 21% of patients with congenital pseudarthrosis of the tibia (CPT) had somatic mono-allelic NF1 inactivation, suggesting a potential role for NF1 in the development of CPT. This represents phenotypic variability in NF1-related conditions.

RANK 3 - LOW PRIORITY

chr17:g.80041061G>A

Gene:	FASN (Fatty Acid Synthase)
Genomic Position:	chr17:80041061 G>A
ClinVar Classification:	Likely benign
Review Status:	Criteria provided, single submitter
Associated Conditions:	Epileptic encephalopathy

Overall Assessment: Low clinical concern due to lack of clear association with neurofibromatosis in literature notes.

Priority Reason: Likely benign ClinVar annotation and low Evo2 delta score (-18.624)

Computational Evidence

Evo2 Delta Score: `-18.624 (moderately negative)`

AlphaGenome Signals:

- **SPLICE_JUNCTIONS:** `0.942`
- **CONTACT_MAPS:** `0.928`
- **CAGE:** `-0.614`
- **CHIP_HISTONE:** `0.553`
- **CHIP_TF:** `0.486`

Key Literature Notes: Studies discuss NF2-Related Schwannomatosis molecular pathology and the role of the Merlin protein in regulating cell growth. Limited direct relevance to NF1 or this specific FASN variant. The variant is associated with epileptic encephalopathy rather than neurofibromatosis.

Methodology & Evidence Framework

Ranking Criteria

Variants were ranked based on multiple lines of evidence:

- **ClinVar Clinical Significance:** Expert-reviewed classifications (Pathogenic > Likely pathogenic > VUS > Likely benign > Benign)
- **Review Status:** Multiple submitter consensus vs. single submitter
- **Disease Relevance:** Direct association with neurofibromatosis phenotype
- **Evo2 Delta Scores:** More negative values suggest larger evolutionary constraint and potential functional impact
- **AlphaGenome Predictions:** AI-predicted regulatory effects on splicing, expression, and chromatin structure
- **Literature Evidence:** Published studies linking variants or genes to neurofibromatosis

Evidence Interpretation Notes

Evo2 Delta Scores: Range from -6.5 to -79.6 in this dataset. More negative scores indicate greater evolutionary constraint violation, suggesting functional impact. The BRCA1 variant has the most extreme score.

AlphaGenome Signals: Values near ±1.0 indicate strong predicted effects. Key tracks include:

- SPLICE_JUNCTIONS/SPLICE_SITES: Impact on RNA splicing
- RNA_SEQ: Predicted expression changes
- CAGE/PROCAP: Transcription start site activity
- CONTACT_MAPS: 3D chromatin organization effects

Clinical Recommendations

1. **Variant chr17:g.41201213T>A (BRCA1):** While classified as pathogenic for hereditary cancer syndromes, this variant is in BRCA1, not NF1. Clinical correlation needed to determine relevance to the patient's neurofibromatosis phenotype. Consider genetic counseling for cancer risk assessment.
2. **Variant chr17:g.29557957G>T (NF1):** Despite "likely benign" classification, this variant is in the NF1 gene and shows some computational signals. Consider in clinical context, particularly if patient has skeletal manifestations. May warrant segregation analysis if familial cases are available.
3. **Variant chr17:g.80041061G>A (FASN):** Not relevant to neurofibromatosis. Likely benign classification and lack of disease association support no further follow-up for NF1 phenotype.

⚠️ **Critical Note:** The original ranking appears to conflate BRCA1 and NF1. While families can carry mutations in both genes, they are distinct loci with different phenotypes. Re-evaluation by a board-certified clinical geneticist or genetic counselor is strongly recommended before clinical action.

Analysis Framework: Multi-evidence clinical genomics assessment

Data Sources: ClinVar, Evo2 conservation scores, AlphaGenome regulatory predictions, Literature review

Report Generated: October 1, 2025

This report is for research and educational purposes. Clinical decisions should be made by qualified healthcare professionals with appropriate genetic counseling.