Neurofibromatosis Type 1 (NF1) Variant Analysis Report

ClinVar Data Analysis - Chromosome 17

Gene: NF1 (Gene ID: 4763)

Date: October 1, 2025

Summary: Analysis of 7 NF1 variants from ClinVar database (GRCh37/hg19 reference). Three pathogenic variants identified with strong clinical evidence (splice site, nonsense, and frameshift mutations). One variant shows conflicting interpretations requiring additional clinical context.

1. Pathogenic Variants (Disease-Causing)

Variant 1: chr17:29654516 G>A

dbSNP ID: rs876660141

Variant Type: Splice acceptor variant

Clinical Significance: Pathogenic

Review Status: Criteria provided, multiple submitters, no conflicts

Molecular Consequence: SO:0001574 (splice acceptor variant)

Clinical Impact: Disrupts normal RNA splicing, likely resulting in aberrant transcript and loss of protein function

Origin: Germline (inherited) and de novo

Variant 2: chr17:29657379 T>A

dbSNP ID: rs2069450324

Variant Type: Nonsense (stop-gain)

Clinical Significance: Pathogenic

Review Status: Criteria provided, single submitter

Molecular Consequence: SO:0001587 (nonsense)

Clinical Impact: Introduces premature stop codon leading to truncated, non-functional protein

Origin: Germline

Variant 3: chr17:29552220 AC>A (1bp deletion)

dbSNP ID: rs1597710675

Variant Type: Frameshift deletion

HGVS: NC_000017.10:g.29552221del

Clinical Significance: Pathogenic

Review Status: Criteria provided, multiple submitters, no conflicts

Molecular Consequence: SO:0001589 (frameshift variant)

Clinical Impact: Frameshift mutation disrupting reading frame and causing protein dysfunction

Origin: Germline

2. Variant with Conflicting Evidence

Variant 4: chr17:29592354 G>A

dbSNP ID: rs876659197

Variant Type: Missense variant

Clinical Significance: **Conflicting classifications**

- Likely pathogenic: 1 submitter
- Uncertain significance: 6 submitters

Review Status: Criteria provided, conflicting classifications

Associated Phenotypes: Neurofibromatosis type 1, Juvenile myelomonocytic leukemia, Cardiovascular phenotype

Note: Requires family segregation studies and additional functional evidence for definitive classification

Origin: Germline

3. Variant of Uncertain Significance (VUS)

Variant 5: chr17:29654553 C>G

dbSNP ID: rs876657714

Variant Type: Missense variant

Clinical Significance: Uncertain significance

Review Status: Criteria provided, single submitter

Molecular Consequence: SO:0001583 (missense variant)

Note: Insufficient evidence to determine pathogenicity; not recommended for clinical decision-making without additional data

Origin: Germline

4. Likely Benign / Benign Variants

Variant 6: chr17:29557957 G>T

dbSNP ID: rs764474296

Variant Type: Intronic variant

Clinical Significance: Likely benign

Review Status: Criteria provided, single submitter

Allele Frequency (ExAC): 0.00001 (1 in 100,000)

Note: Located in intron; unlikely to affect protein function

Variant 7: chr17:29684304 T>C

dbSNP ID: rs767860040

Variant Type: Synonymous variant

Clinical Significance: Likely benign

Review Status: Criteria provided, multiple submitters, no conflicts

Allele Frequency (ExAC): 0.00001 (1 in 100,000)

Molecular Consequence: SO:0001819 (synonymous variant)

Note: Silent mutation; does not change amino acid sequence

5. Summary Table

Position	Change	Type	Significance	dbSNP
29654516	G>A	Splice acceptor	**Pathogenic**	rs876660141
29657379	T>A	Nonsense	**Pathogenic**	rs2069450324
29552220	AC>A	Frameshift	**Pathogenic**	rs1597710675
29592354	G>A	Missense	**Conflicting**	rs876659197
29654553	C>G	Missense	Uncertain	rs876657714
29557957	G>T	Intronic	Likely benign	rs764474296
29684304	T>C	Synonymous	Likely benign	rs767860040

6. Key Clinical Insights

- **Loss-of-function mutations predominate:** The pathogenic variants include splice site, nonsense, and frameshift mutations, all resulting in loss of NF1 protein (neurofibromin) function
- **Haploinsufficiency mechanism:** NF1 acts as a tumor suppressor gene; one mutated copy is sufficient to increase disease risk through reduced neurofibromin levels
- **Mutation spectrum:** The variety of mutation types reflects the large size of the NF1 gene and multiple mechanisms of pathogenicity
- **Conflicting evidence:** The missense variant at position 29592354 requires additional clinical context, segregation data, and functional studies for definitive interpretation
- **Phenotypic variability:** Some variants are associated with additional features beyond classic NF1, including cardiovascular abnormalities and increased risk of juvenile myelomonocytic leukemia
- **Clinical testing considerations:** Pathogenic variants should be confirmed with orthogonal methods; VUS results require genetic counseling regarding limitations

7. Recommendations

- Pathogenic variants (positions 29654516, 29657379, 29552220) are reportable findings consistent with NF1 diagnosis
- The conflicting variant (29592354) should be classified as VUS unless additional evidence becomes available
- Variants of uncertain significance should not be used alone for clinical decision-making
- Genetic counseling is recommended for all patients with NF1-related findings
- Regular monitoring according to NF1 clinical guidelines is appropriate for confirmed pathogenic variant carriers

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Data Source: ClinVar VCF file (GRCh37/hg19 reference assembly)

Reference Genome: GRCh37 (hg19)

Analysis Date: October 1, 2025

Note: This report is for research and informational purposes. Clinical interpretation should be performed by qualified healthcare professionals with appropriate genetic counseling.