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A Case Report of Neurofibromatosis Type 1 Caused by NF1 Gene Mutation

Liyang Duan
The Second Affiliated Hospital, Zhejiang University School of Medicine
Tianyi Ming
The Second Affiliated Hospital, Zhejiang University School of Medicine
Xianjie Wu
wuxianjie@zju.edu.cn

The Second Affiliated Hospital, Zhejiang University School of Medicine

Case Report

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Abstract

Background

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem disorder caused by pathogenic variants in the NF1 tumor suppressor gene at 17q11.2. The gene encodes neurofibromin, a negative regulator of RAS signaling, yet the molecular basis of the striking clinical variability remains incompletely elucidated. Approximately half of cases arise from de novo mutations.

Methods

We retrospectively analyzed the clinical records, cranial MRI, histopathology, and genetic data of a 16-year-old male with suspected neurofibromatosis type 1. Whole-exome sequencing of the proband and targeted Sanger sequencing of his unaffected parents were conducted to characterize the *NF1* variant and its inheritance.

Results

A 16-year-old male with numerous café-au-lait macules, axillary freckling, and cutaneous neurofibromas met clinical criteria for NF1. Genetic testing revealed a novel heterozygous NF1 frameshift variant, c.2619dupT (p.Lys874*), which was absent in his unaffected parents, confirming its de novo origin. Cranial MRI showed T2 hyperintensities in the left basal ganglia and bilateral thalami and hippocampi. At six months, the patient remained stable without evidence of disease progression.

Conclusions

This report documents a novel *de novo* frameshift variant in the *NF1* gene identified in a patient with classic features of neurofibromatosis type 1. The characterization of previously unreported pathogenic alleles expands the known mutational repertoire of *NF1* and provides additional data to refine genotype-phenotype correlations, ultimately supporting more accurate molecular diagnosis and genetic counseling in this complex disorder.

Introduction

Neurofibromatosis type 1 (NF1; MIM 162200) is a common autosomal dominant disorder with complete penetrance and highly variable expressivity, with an estimated incidence of 1/2000 to 1/3000[1]. It is caused by mutations in the NF1 tumor suppressor gene at 17q11.2, which encodes neurofibromin, a negative regulator of the RAS/MAPK pathway. Over 2600 intragenic variants have been reported, with no clear mutational hotspots[2]. Clinical manifestations primarily involve the skin, nervous system, and

skeleton, including café-au-lait macules, neurofibromas, and an increased risk of malignancy. Genotype-phenotype correlations remain complex and incompletely understood.

Case Presentation

A 16-year-old male patient presented with multiple café-au-lait macules (CALMs) distributed across his entire body. The lesions first appeared on the trunk four years prior and had progressively increased in number. He denied any history of epilepsy, headache, malignancy, visual impairment, gait difficulty, intellectual disability, or scoliosis.

Physical examination revealed normal intelligence and development, along with multiple dermatological findings. These included numerous CALMs of varying sizes (largest > 10 cm, smallest 1 mm) scattered over the body, without pruritus or pain; two palpable nodules on the right upper limb; one nodule on the occipital region; and a soft, non-tender, well-demarcated cutaneous mass with a "balloon-like" consistency under the left breast (Fig. 1).

Cranial magnetic resonance imaging (MRI) showed abnormal signals in the left basal ganglia, bilateral thalamus, and hippocampus. Histopathological examination of a skin lesion demonstrated aggregates of spindle cells arranged in a wavy pattern within the dermis, consistent with neurofibroma (Fig. 2). Whole-exome sequencing identified a heterozygous frameshift mutation in the NF1 gene (c.2619dupT, p.Lys874*). Genetic testing of the parents confirmed the de novo origin of this mutation. There was no family history of similar conditions, and the parents were non-consanguineous(Fig. 3).

Based on the revised diagnostic criteria from the international consensus recommendation (2021)[3], a diagnosis of neurofibromatosis type 1 (NF1) was established. As the cutaneous lesions were asymptomatic, no active treatment was initiated. The patient was advised to undergo regular annual follow-up, including physical and ophthalmological examinations, to monitor for disease progression or complications.

Discussion

Over 2600 NF1 mutations have been reported, the vast majority (90–95%) being intragenic variants, including missense, nonsense, splice-site, and frameshift mutations, while fewer than 10% represent whole-gene deletions; no clear mutational hotspots have been identified. Several well-established genotype-phenotype correlations have emerged. For example, 17q11.2 microdeletions are associated with a severe phenotype featuring numerous neurofibromas, intellectual disability, dysmorphic features, and an elevated risk of malignant peripheral nerve sheath tumors (MPNST). Missense variants in codons 844–848 similarly confer a high burden of symptomatic plexiform neurofibromas and MPNST. Conversely, the in-frame deletion p.Met992del and missense substitutions at p.Arg1809 are linked to mild phenotypes characterized predominantly by pigmentary manifestations, with an absence of

neurofibromas and optic pathway gliomas. Truncating mutations such as frameshifts generally result in complete loss of neurofibromin function and are typically associated with classic, full-blown NF1[1,4].

The novel frameshift variant identified in this patient, c.2619dupT (p.Lys874*), introduces a premature termination codon at amino acid position 874, upstream of the catalytically essential GRD (residues approximately 1198–1530), thereby truncating the protein before this critical domain is synthesized. This variant is absent from population databases and has not been previously described. Located in exon 20 within the GRD-encoding region, it satisfies ACMG/AMP criteria (PVS1, PS3, PM2) for a pathogenic classification. The premature termination codon is predicted to abolish neurofibromin GAP activity, leading to constitutive RAS/MAPK pathway activation and a molecular environment permissive for tumorigenesis.

Despite this predicted severe molecular profile, the patient exhibited a relatively mild phenotype limited to café-au-lait macules, axillary freckling, and cutaneous neurofibromas, without plexiform tumors, skeletal defects, or intracranial neoplasms at presentation. This discordance between the expected classic phenotype and the observed attenuated presentation may be explained by several factors. Tissue-specific somatic second-hit mutations may have occurred only in a restricted population of Schwann cells, limiting disease manifestations to the skin. Alternative splicing might partially bypass the premature termination codon, enabling residual production of a partially functional neurofibromin that tempers clinical severity. Modifier genes such as SPRED1, which encodes a negative regulator of the RAS/MAPK pathway, could exert compensatory effects, mirroring the mild pigmentary-only phenotype observed in Legius syndrome. Finally, the patient's young age is a critical consideration, given the well-documented age-dependent penetrance of many NF1-associated complications, including plexiform neurofibromas and MPNST.

This case expands the NF1 mutational spectrum and underscores that even truncating variants predicted to be highly damaging can manifest as attenuated phenotypes. It reinforces the importance of individualized long-term surveillance irrespective of initial severity and contributes to refining the understanding of genotype-phenotype heterogeneity in NF1.

Declarations

Ethics approval and consent to participate

This retrospective case report involved only the use of anonymized clinical data obtained from routine clinical practice, with no prospective intervention. The Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China waived the need for ethics approval for this case report. Written informed consent was obtained from the patient's parent/legal guardian for participation. The study was conducted in accordance with the ethical guidelines of the institution and the Declaration of Helsinki.

Consent for publication

Written informed consent for publication of the clinical data, photographs, and genetic information was obtained from the patient's parent/legal guardian. A copy of the signed consent form is available upon request.

Author Contribution

Liyang Duan wrote the main manuscript text. Tinayi Ming performed data organization, and Xianjie Wu provided essential information. All authors reviewed the manuscript.

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Figures

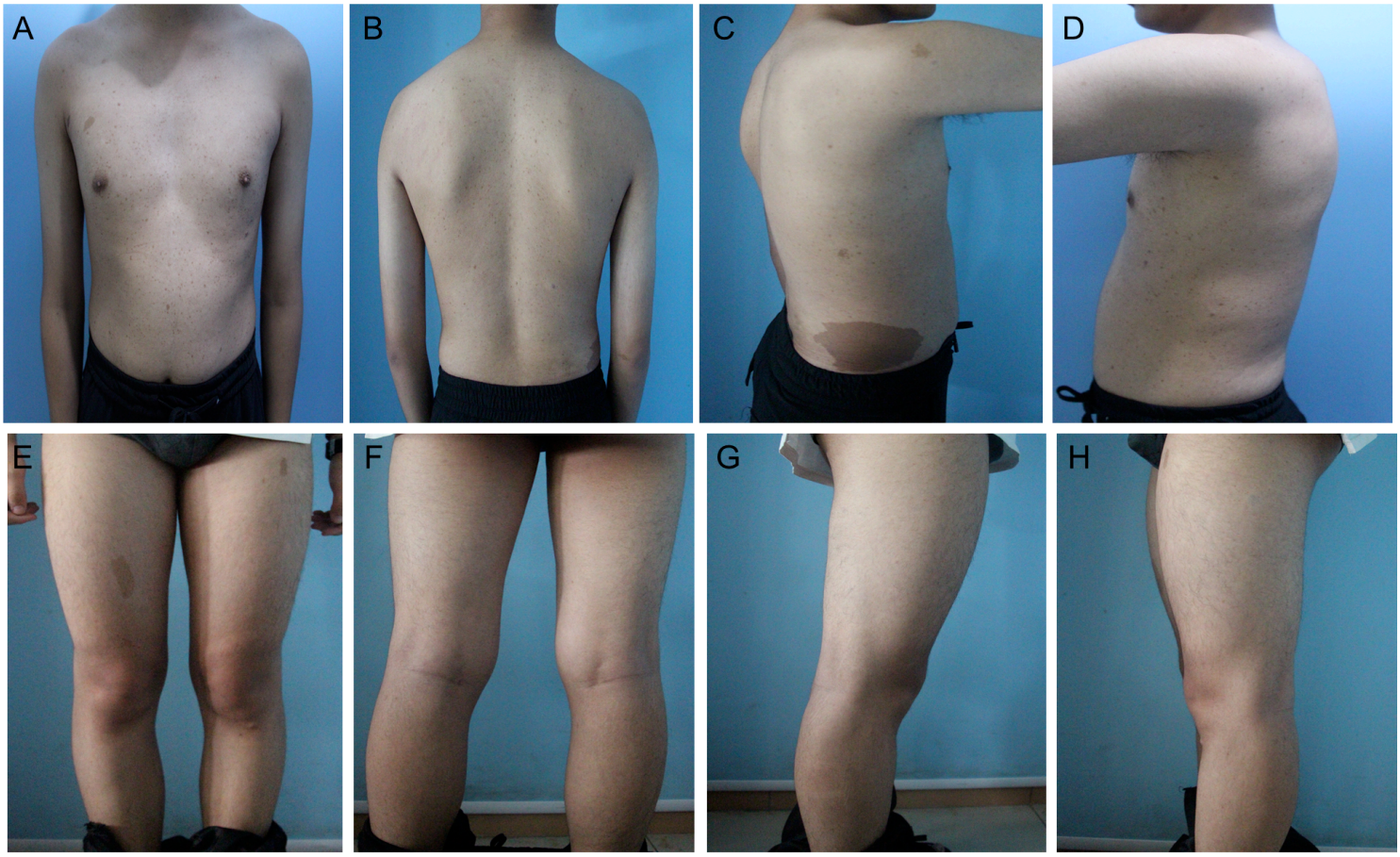


Figure 1

Clinical features of the patient: (A-H) Multiple café-au-lait macules of various sizes distributed over the trunk and limbs.

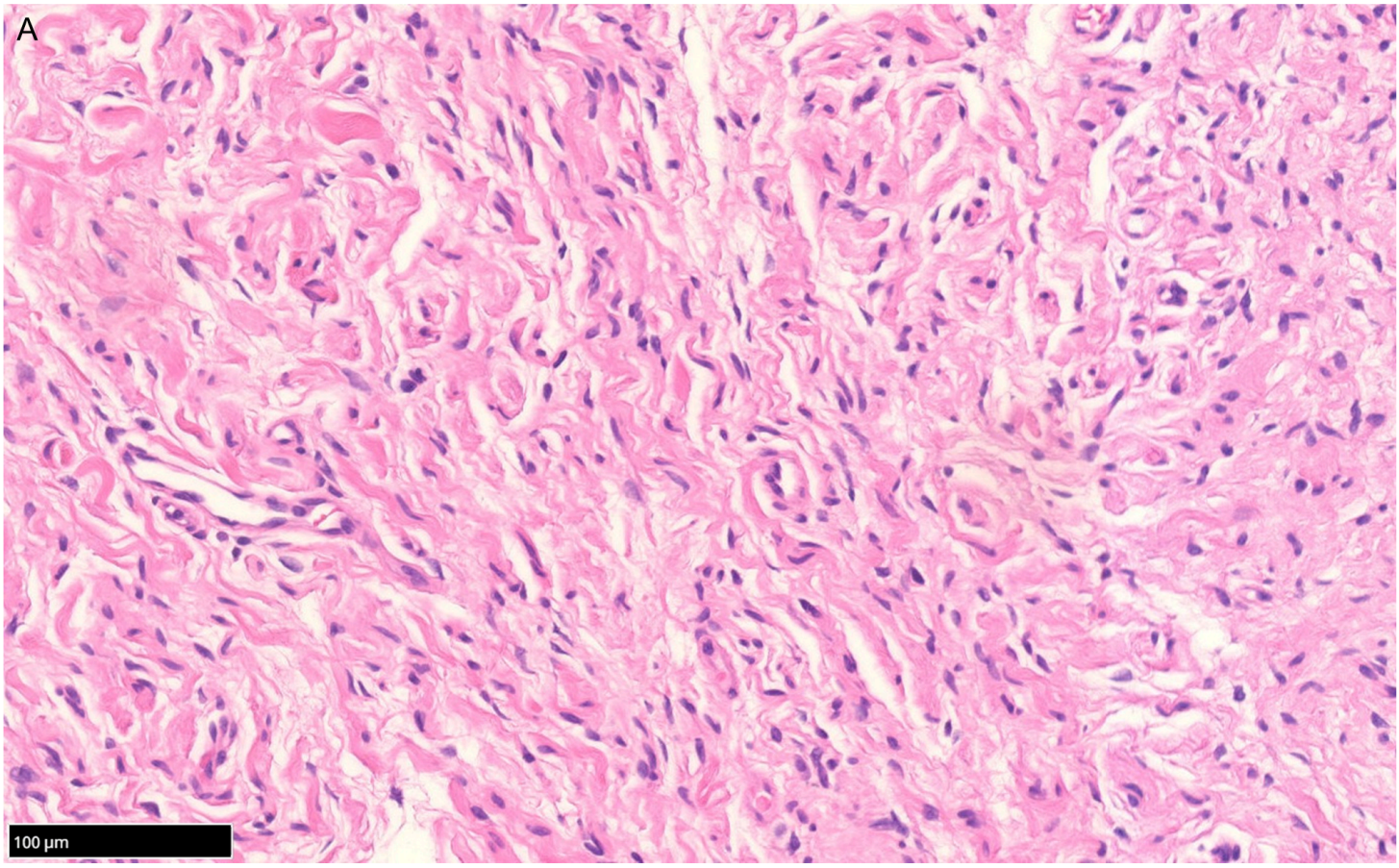


Figure 2

Histopathology of the subcutaneous nodule: (A) Hematoxylin and eosin (H&E) staining of the excised subcutaneous nodule reveals a proliferation of spindle cells with wavy, comma-shaped nuclei, arranged in fascicles within the dermis. Original magnification, ×20. Scale bar, 100µm.

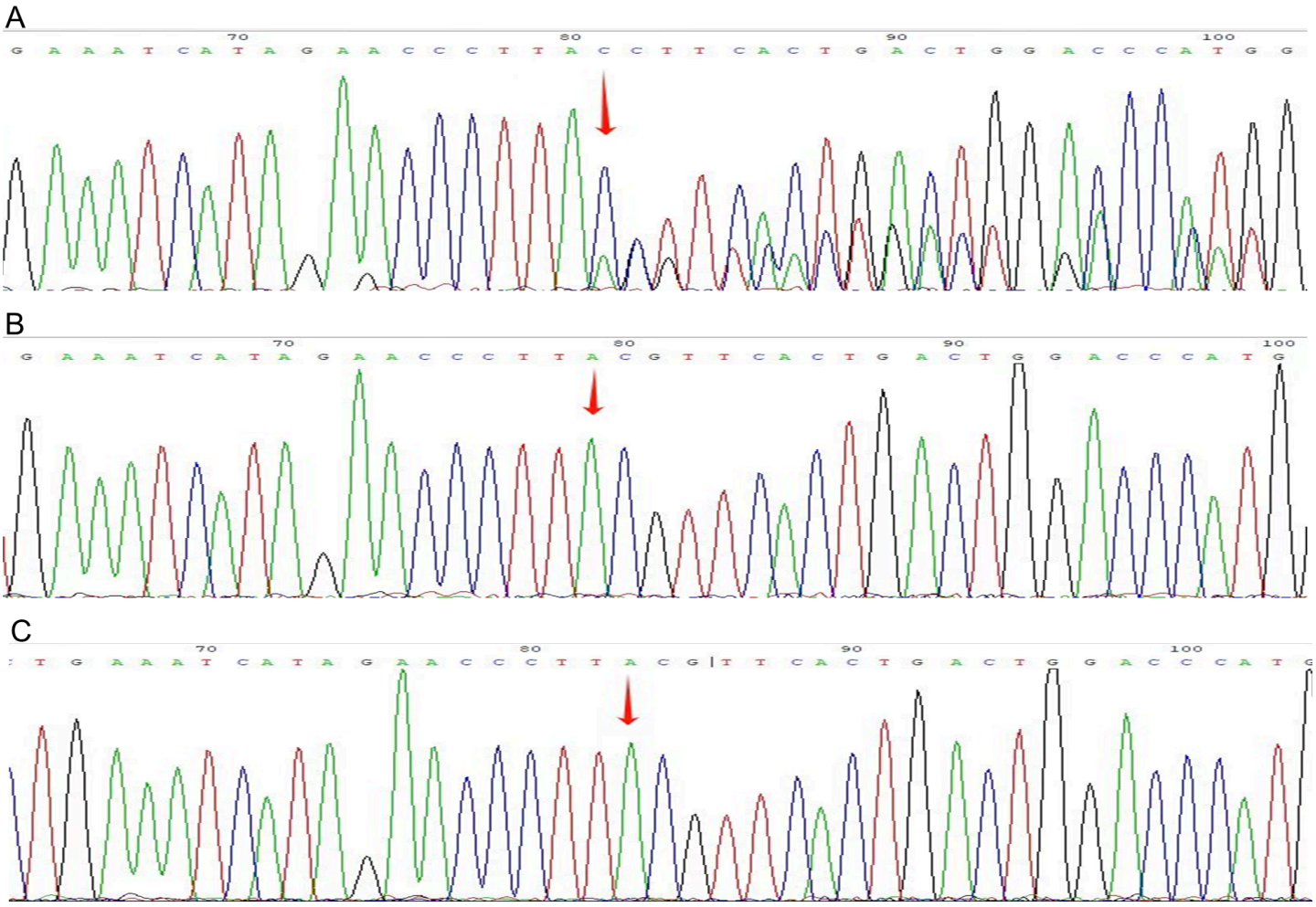


Figure 3

Whole-exome sequencing and parental validation of the *NF1* mutation: (A) Proband: heterozygous frameshift mutation c.2619dupT (p.Lys874*), identified by whole-exome sequencing. (B) Mother and (C) father: wild-type sequences at the corresponding site.