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Original Article

A case of neurofibromatosis type 1 caused by a novel NF1 mutation

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Abstract

Neurofibromatosis type 1 is an autosomal dominant disorder caused by loss-of-function mutations in the *NF1* gene, leading to constitutive Ras pathway activation. *NF1* gene mutations exhibit complete penetrance, cause high phenotypic variability, and feature diverse types without established hotspots. This study identified a novel pathogenic variant via whole-exome sequencing in a pediatric case, broadening the spectrum of known *NF1* mutations. We further describe the clinical response to the MEK inhibitor selumetinib, including regression of subcutaneous nodules, with no significant improvement in cutaneous neurofibroma scores was observed.

Key words: Neurofibromatosis type 1, *NF1*, genotype–phenotype association, selumetinib

1. Clinical data

The patient is a 10-year-old male with an unremarkable family and birth history. His clinical symptoms began at approximately 2 years of age with the appearance of multiple café-au-lait macules (CALMs) on the trunk and limbs, which progressed in number and size. At age six, he developed axillary and inguinal freckling, followed by the emergence of multiple, tender, and progressively enlarging subcutaneous nodules on the upper limbs and neck at age seven.

Physical examination (Fig. 1) revealed numerous well-defined CALMs, 0.5–1.5 cm in diameter, scattered across the body. Over 20 firm, well-defined, and mobile subcutaneous nodules, ranging in size from approximately 0.5 to 3.0 cm, were observed on the upper limbs, neck, chest, back, and lumbar region.

Brain MRI demonstrated multiple unidentified bright objects (UBOs) without associated neurological symptoms or abnormalities. Whole-body imaging revealed extensive neurofibroma involvement, including multiple small nodules distributed along the spinal axis, peripheral nerves, and a characteristic plexiform neurofibroma (pNF) inferior to the left sacroiliac joint (Fig. 2). No iris abnormalities, skeletal deformities, or other systemic diseases were detected. Routine laboratory studies were unremarkable.

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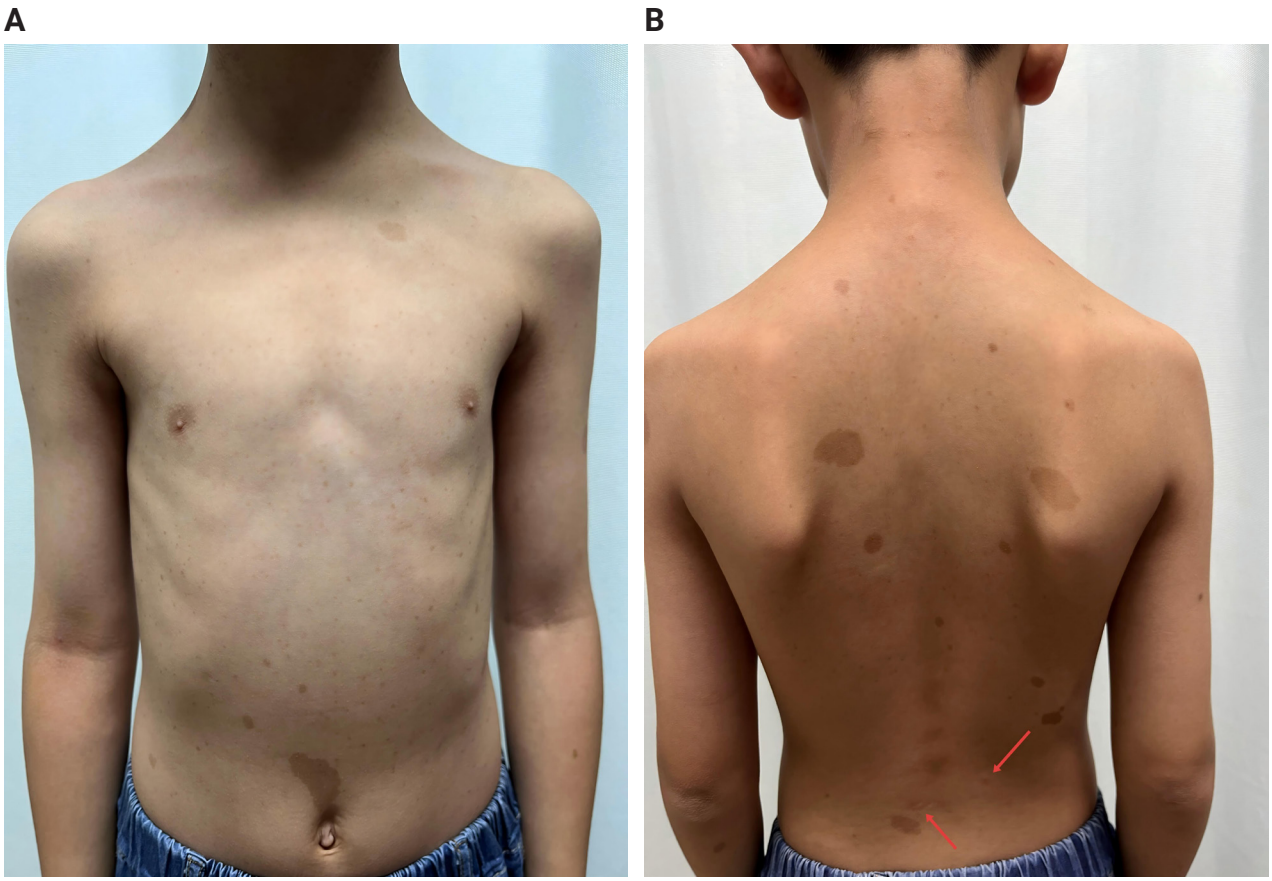

Figure 1. Clinical photographs of the patient. **A)** CALMs on the chest and abdomen. **B)** CALMs and subcutaneous nodules on the back.

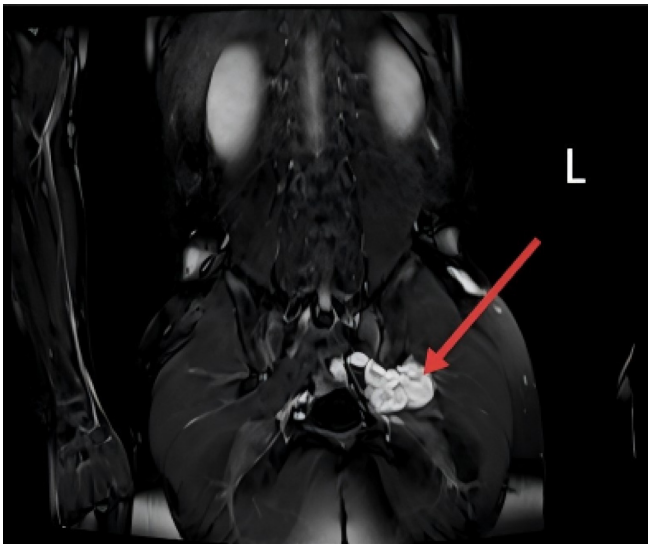

Figure 2. Coronal T2-weighted fat-suppressed MRI showing the plexiform neurofibroma located inferior to the left sacroiliac joint.

2. Whole-exome and Sanger sequencing results

Whole-exome sequencing identified a *de novo NF1* variant, c.7926_7927dup (p.Lys2643Ilefs*16), which was confirmed by Sanger sequencing to be absent in both parents (Fig. 3). This variant is unreported in pathogenic mutation databas-

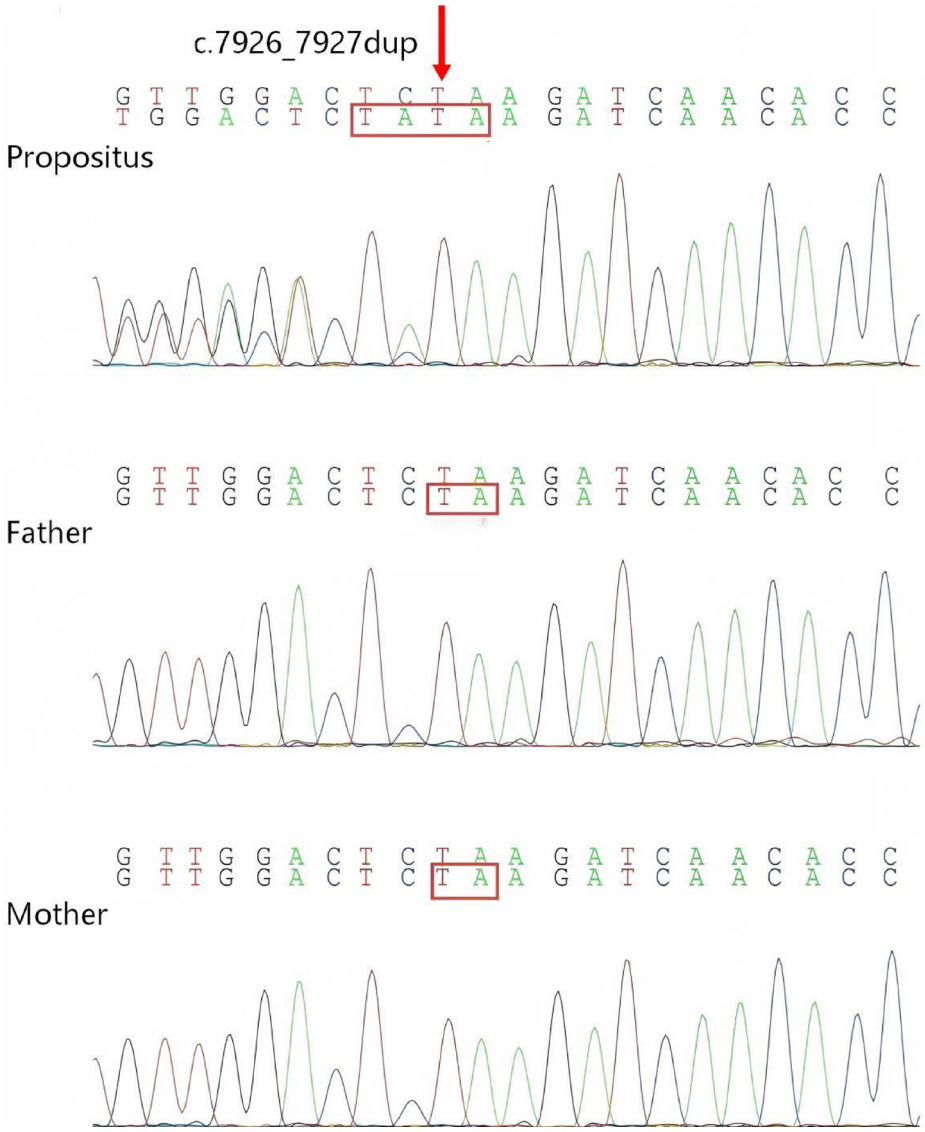

Figure 3. Sanger sequencing results c.7926_7927dup (NM_000267): 2-bp tandem duplication of 5'-TA-3', causing a frameshift (p.Lys2643Ilefs*16).

es (e.g., HGMD Pro, ClinVar) and absent from healthy population cohorts (e.g., ExAC, 1000 Genomes), supporting its classification as a novel pathogenic mutation. This mutation alters the reading frame from codon 2643 (p.Lys2643Ile), leading to a premature stop codon 16 residues downstream (p.Lys2643Ilefs*16) and a truncated protein lacking 159 C-terminal amino acids. The mutant transcript is likely subject to nonsense-mediated mRNA decay, resulting in loss of function. The variant was absent in population databases (PM2_Supporting).

3. Treatment

The patient had received no prior disease-modifying therapy for NF1-related neurofibromas. Given the presence of progressive subcutaneous and plexiform neurofibromas, and the established role of MEK inhibition in downregulating the aberrant RAF/MEK/ERK signaling downstream of NF1 loss-of-function, selumetinib was initiated at 25 mg/m^2 twice daily following the standard pediatric dosing regimen for NF1-related plexiform neurofibromas [1]. Following four

months of selumetinib treatment, the patient demonstrated regression of subcutaneous nodules, despite no significant change in cutaneous neurofibroma scores on the Nef-ASI scale [2]. This differential response is consistent with recent findings [3]. Nevertheless, given the need to control progression of the pNF, the patient continued selumetinib treatment beyond the four-month period with ongoing monitoring. During follow-up, the patient developed adverse effects including xerosis and rash.

4. Discussion

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by pathogenic variants in the *NF1* gene, leading to dysfunction of its protein product, neurofibromin [4]. With an estimated prevalence of 1 in 3,000 to 1 in 4,000, NF1 typically presents from early childhood with clinical features such as CALMs, neurofibromas, Lisch nodules of the iris, and skeletal abnormalities [5]. The *NF1* gene is located on chromosome 17q11.2 and comprises 61 exons encoding neurofibromin, a 2,818-amino acid Ras GTPase-activating protein (Ras-GAP) [6,7]. Loss-of-function mutations in *NF1* result in constitutive activation of the Ras signaling pathway, dysregulating downstream pathways such as PI3K/AKT/mTOR and RAF/MEK/ERK [8].

NF1 exhibits significant genetic heterogeneity, with over 50% of cases arising from *de novo* mutations. More than 4,600 pathogenic variants have been documented, with no defined mutational hotspots [6]. Emerging genotype-phenotype correlations provide insights into the disease variability: specific missense variants such as p.Arg1809 are linked to a milder presentation, while alterations at codons 844–848, p.Arg1276, and p.Lys1423 are associated with more severe phenotypes [9]. In our patient, the c.7926_7927dup variant in exon 54 introduces a premature termination codon. Although located in the non-catalytic C-terminal domain, this truncation is predicted to impair neurofibromin stability and function, likely explaining the observed clinical features including CALMs and pNF.

This case, diagnosed via whole-exome sequencing, identifies a novel *NF1* mutation (c.7926_7927dup) that broadens the spectrum of known pathogenic variants and providing preliminary genotype-phenotype data for this unreported C-terminal truncating variant. Furthermore, it reports the early clinical response to the MEK inhibitor selumetinib, and offers reference evidence for clinical management.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical approval

This study was approved by the Institutional Review Board of Guangzhou Dermatology Hospital (Ethics approval number: gzsp202251). Written informed consent was obtained from the patient's legal guardians for study participation and for publication of clinical images and related clinical data. All study procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Ethical statement

The authors declare, that no clinical trials with human participation and/or use of human material (e.g., tissues, commercially available cell lines, blood, serum, etc.) were performed.

The authors declare that no animal studies and/or experiments with/on animals were performed.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.

No artificial-intelligence-assisted tools were applied for data generation, image processing, statistical analysis, or manuscript drafting and revision in this work.

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Author contributions

Fengmei He and Xin Zhou contributed equally and are co-lead authors.
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Data availability

All of the data that support the findings of this study are available in the main text.