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A Case of Neurofibromatosis Type 1 Caused by a Novel NF1 Mutation

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Introduction
Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by pathogenic variants in the *NF1* gene, here we reported a novel *de novo* frameshift insertion (c.7926_7927ins[base]) in the *NF1* gene inducing the phenotype of neurofibromatosis type 1.

Materials and Methods
The patient is a 10-year-old male with a non-contributory family and birth history. His clinical presentation 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 brown macules, 0.5-1.5 cm in diameter, scattered across the body. Over 20 firm, well-defined, and mobile subcutaneous nodules, ranging in size from soybean to red date, were observed on the upper limbs, neck, chest, back, and lumbar region. No iris abnormalities, skeletal deformities, or other systemic diseases were detected.Routine laboratory studies were unremarkable. Brain MRI demonstrated multiple unidentified bright objects (UBOs), characteristic of neurofibromatosis. 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.

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. 2). This variant is unreported in pathogenic mutation databases (e.g., HGMD Pro, ClinVar) and absent from healthy population cohorts (e.g., EXAC, 1000 Genomes), supporting its classification as a novel pathogenic mutation. A novel *de novo* frameshift insertion (c.7926_7927ins[base]) was identified in the *NF1* gene. 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 subjected to nonsense-mediated mRNA decay, resulting in loss of function. The variant was absent in population databases (PM2_Supporting). Following four months of selumetinib treatment, the patient demonstrated regression of subcutaneous nodules, indicating a clinical benefit, despite no significant change in cutaneous neurofibroma scores on the Nef-ASI scale.

Conclusions
This case, diagnosed via whole-exome sequencing, identifies a novel *NF1* mutation that broadens the spectrum of known pathogenic variants and enhances the understanding of genotype-phenotype correlations. Furthermore, it

corroborates existing evidence that selumetinib can effectively control neurofibroma growth and induce tumor regression with a favorable safety profile.