

A Novel Frameshift Mutation in Neurofibromin 1 Gene in a Chinese Family with Neurofibromatosis Type 1

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To the Editor: Neurofibromatosis type 1 (NF1) is a common autosomal dominant genetic neurocutaneous disorder mainly characterized by café-au-lait macules (CALMs), neurofibromas, skinfold freckling, and Lisch nodules.^[1] Mutations in the neurofibromin 1 gene (*NF1*) are known to solely result in NF1.^[1] Most NF1 patients with mutations in *NF1* are sporadic cases; the mean proportion of familial ones is approximately 31.8% with a range from 13.0% to 45.8%.^[2-4] The mutation analysis of *NF1* remains difficult due to the large size and complexity of the gene.^[5] The direct DNA sequence analysis is a conclusive approach to establishing the molecular diagnosis of NF1. Here, we report a novel frameshift mutation in *NF1* gene in a Chinese nuclear family with NF1.

The proband, a 43-year-old female, was born with CALMs and developed skinfold freckling at the age of 5 years. These skin pigmentation spots increased in number in early childhood. At the age of 8 years, the proband presented cutaneous and subcutaneous soft nodules on the trunk, which progressively distributed all over the body before adulthood. A physical examination revealed more than 100 differently sized cutaneous and subcutaneous neurofibromas over the face, limbs, and trunk accompanied by dozens of scattered CALMs, and skinfold freckling [Figure 1a]. The proband's son (II-1) was a 21-year-old male with milder lesions manifested by a few barely visible subcutaneous neurofibromas and several smaller CALMs on his trunk [Figure 1b] and extremities. No intelligence abnormality, short stature, distinctive bone deformities, visual disturbances, and peripheral nervous system symptoms and signs were found in either case. The proband's male counterpart was healthy and did not report a similar abnormal phenotype among other relatives. The pedigree of this NF1 family is shown in Figure 1c. The direct sequencing of genomic DNA was performed in all the three family members and 100 unrelated healthy controls. The verification of subsequent two-directional sequencing revealed a heterozygous frameshift mutation, c.6547_6548insA (p.T2183NfsX38) on exon 42 in *NF1* gene, identified in the proband and her affected progeny, but not in her spouse and 100 unrelated healthy controls [Figure 1d]. Moreover, the protein sequence alignment showed a high degree of conservation of the amino acid sequence around the T2183 residue in the neurofibromin protein across 12 different species by the UCSC Genome Bioinformatics

tool [Figure 1e]. In addition, this *NF1* mutation has not been included in the Human Gene Mutation Database (HGMD), the *NF1* Leiden Open Variation Database, and literatures on PubMed. Thus, it was considered a novel mutation.

Herein, we present a case of a Chinese NF1 family with a novel mutation in *NF1* gene. The diagnosis of NF1 was made in the proband and her male progeny based on their typical clinical presentations characterized by neurofibromas and CALMs, with or without skinfold freckling.^[1] NF1 has an extreme and unpredictable clinical variability, even among affected individuals with the same mutation and within a single family.^[1,5] This NF1 family also showed the inter-individual phenotypic variation. The proband and her affected son presented a different number, type, and distribution of neurofibromas, as well as various features of skin pigmentation when they reached adulthood. Some factors such as a second hit and modifier genes might underlie the variable expression of NF1 within the members of this family.^[1,5]

The *NF1* is a tumor suppressor gene encoding a RAS GTPase-activating protein called neurofibromin, which is a large multi-domain 2818 amino acid protein.^[5] Hitherto, more than 2000 various causative mutations of *NF1* gene associated with NF1 have been recorded in the HGMD database including missense, nonsense, splice-site, and frameshift mutations. However, only approximately 11% of them are frameshift mutations caused by microinsertions. This novel *NF1* mutation (c.6547_6548insA) is predicted to disturb 38 amino acids starting from the threonine (T) residue at position 2183 of the neurofibromin protein and truncate the protein by 599 amino acids (p.T2183NfsX38). This results in a variant neurofibromin protein that loses the maximum portion of the carboxy-terminal domain and the entire syndecan-binding domain.^[5] Although

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Received: 27-10-2016 **Edited by:** Li-Min Chen

How to cite this article: Dong YY, Zhang YH, Li HW, Chen LZ, Wang TM, Hu W, Hu M, She QY, Liu DX, Deng YH. A Novel Frameshift Mutation in Neurofibromin 1 Gene in a Chinese Family with Neurofibromatosis Type 1. Chin Med J 2017;130:629-30.

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DOI:
10.4103/0366-6999.200538

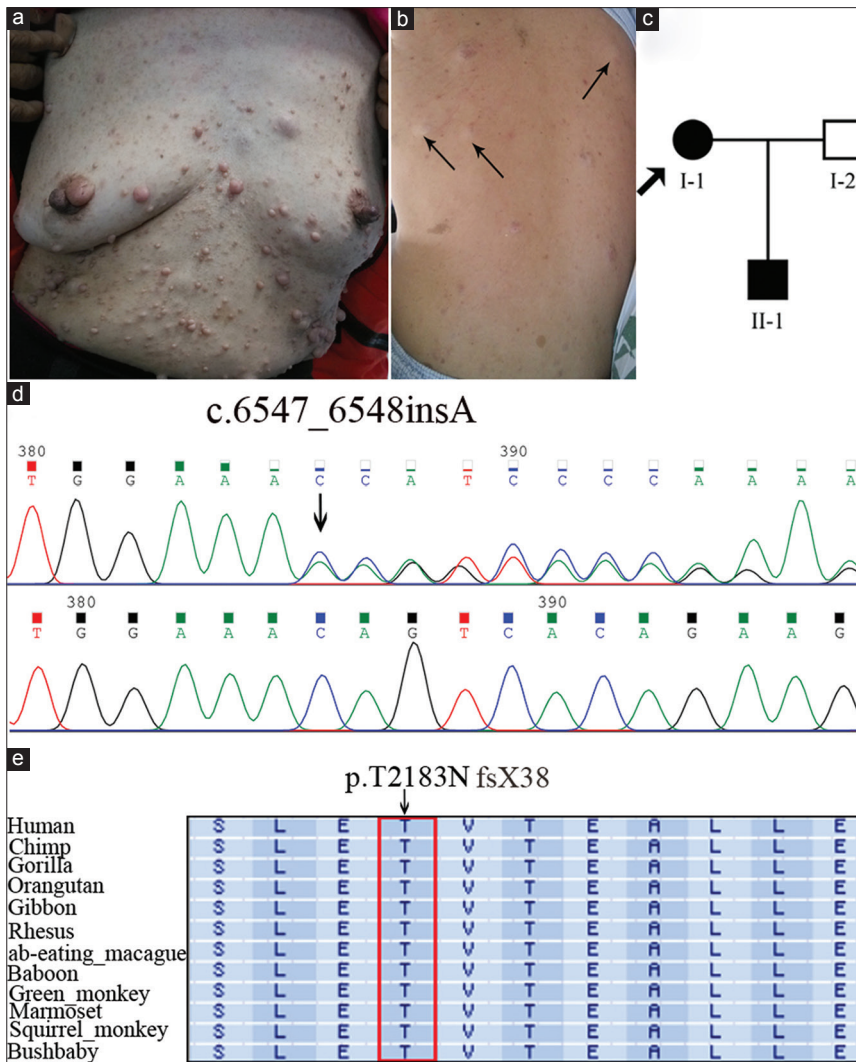


Figure 1: Clinical manifestations and genetic finding in the NF1 family. (a) A number of cutaneous and subcutaneous neurofibromas and CALMs over the front trunk of the proband (I-1). (b) Several subcutaneous neurofibromas (arrow) and CALMs on the back of her son (II-1). (c) Pedigree of this NF1 family. (d) The sequencing result shows a mutation in *NF1* in the proband (I-1) and her son (II-1). (e) Protein alignment shows high conservation of the amino acid sequence around the T2183 residue (in the red box) across 12 different species. NF1: Neurofibromatosis type 1; CALMs: Café-au-lait macules.

the function of these two domains remains to be elucidated, multiple sequence alignment across 12 different species showed a high degree of conservation around the T2183 residue of the neurofibromin protein within this region [Figure 1e], indicating its importance and the potential pathogenicity in the case of mutation. More than 80% of disease-causing *NF1* mutations are truncating mutations,^[4] which are expected to result in haploinsufficiency of the neurofibromin due to the nonsense-mediated mRNA decay (NMD),^[4] the absence of functional domains, or the degradation of the truncated proteins. This might explain the onset of NF1 in this family due to the *NF1* mutation (c.6547_6548insA).

In conclusion, by direct DNA sequencing, we identified a novel causative *NF1* mutation (c.6547_6548insA) in a Chinese family with NF1. The data add to the database of *NF1* gene mutations associated with NF1.

Financial support and sponsorship

This study was supported by a grant from the National Natural Science Foundation of China (No. 81371728).

Conflicts of interest

There are no conflicts of interest.

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