

Novel *in-frame deletion* mutation c.177_179delTAC of neurofibromatosis type 1 in a Chinese 4-year-old boy with binocular blindness

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Dear editor,

I am Dr. Jie Peng, from the Department of Ophthalmology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. I write to present a case report of a novel *in-frame deletion* mutation c.177_179delTAC of neurofibromatosis type 1 in a Chinese boy with bilateral blindness.

Neurofibromatosis type 1 (NF1; OMIM#162200), an autosomal dominant disease, is caused by mutations in the *NF1* gene. The incidence of this disease is around 1 in 3500 individuals [1]. Clinical manifestations include café-au-lait (CAL) spots, cutaneous or subcutaneous neurofibromas, axillary or inguinal freckling, Lisch nodules of the iris, bone dysplasia, optic pathway glioma (OPG), plexiform neurofibromas, learning difficulties, skeletal abnormalities *etc* [2]. The *NF1* gene mapped at chromosome 17q11.2, encoding neurofibromin [3]. Until now, more than 1000 mutations of *NF1* gene have been reported to be connected to NF1 worldwide.

This study was approved by Ethical Committee of Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine and was conducted in accordance with the principles of the Declaration of Helsinki.

A 4-year-old Chinese boy complained of eye redness and

vision loss two weeks after the vaccination against Japanese B encephalitis. He initially was diagnosed of bilateral optic neuritis at local hospital. Anti-virus drugs and steroids were given and not effective. Two months after, he reported to us with no light perception and mild exophthalmos. Fundus images by Retcam III (Clarity, USA) (Figure 1A, 1B) showed binocular optic disc greyish mass. That of the left eye is much bigger with an approximate diameter of 3 PD. Ocular B-ultrasound showed high echogenic mass around the optic disc. Magnetic resonance imaging (MRI) showed bilateral optic nerve and chiasma thickening, multiple hyperplasia lesions in the brainstem, thalamus and capsula interna. Flash-visual evoked potential test revealed almost no P2 wave. This boy also presented with CAL spots on the trunk and extremities with a diameter of 0.2-2.5 cm (Figure 1C). Many of these CAL spots were found at birth and extended gradually. Growth retardation was also detected. No subcutaneous neurofibromas or Lisch nodules were found. While his mother suffered from multiple subcutaneous neurofibromas and CAL spots almost all over the body. She was short in stature and had learning disabilities. Slit-lamp lens examination showed Lisch nodules (Figure 1D). She had a normal vision acuity of 5.0 and a normal fundus. No other family members suffered from similar situations.

After written consent, genomic DNA was extracted from the boy and his mother's peripheral blood lymphocytes. Direct DNA sequencing was done as previously reported [4] and revealed a 3-bp *in-frame deletion* mutation (c. 177_179delTAC) in exon 2 of *NF1* gene (Figure 2) in two patients, which was not found in any of the 100 healthy controls. The novel mutation resulted in deletion of Threonine (p. 60 del Tyr) in exon 2. Majority (60%-70%) of the *NF1* gene mutations are found resulting in protein truncation and those mutations in patients with OPGs probably produce truncated NF1 protein [5]. Our study coordinates with the former study.

The proband complained of binocular blindness, and presented with OPGs involving optic nerve, chiasm and postchiasm structures. OPGs occur in 15% to 20% in NF1 patients [6]. Chance of vision loss among pediatric NF1 patients depends on the tumor extent and location by MRI and is strongly associated with postchiasm involvement [7]. Prevalence of vision loss of OPGs ranges from 20% to

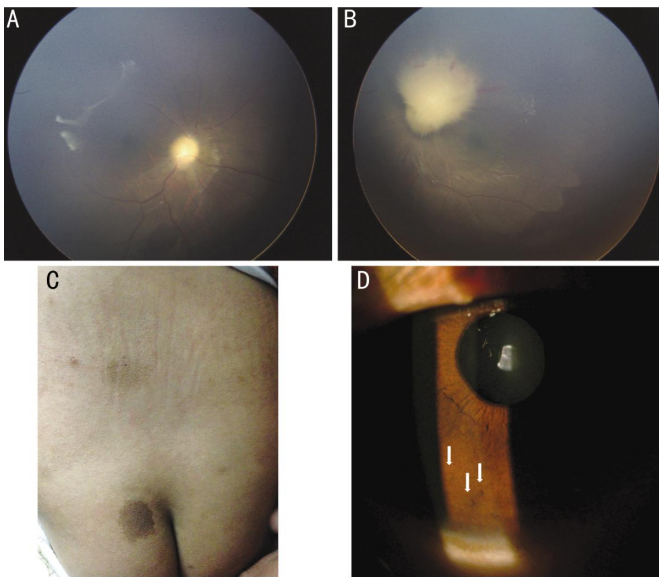


Figure 1 Clinical manifestations of the patients A: Fundus image of the right eye of the boy; B: Fundus image of the left eye of the boy; C: CAL spots of the boy on the trunk; D: Lisch nodules of the mother (white arrow).

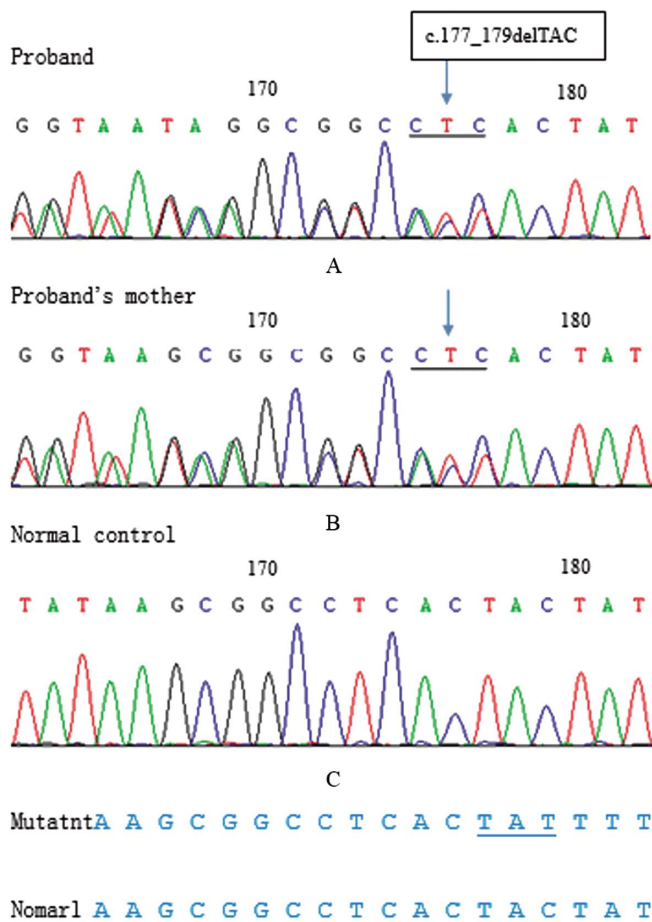


Figure 2 Genomic DNA sequencing by using reverse primer in exon2 showed a germline mutation c. 177_179delTAC (the blue arrow) in proband and his mother, which cannot be found in 100 normal controls.

70%^[6,7]. To our best knowledge, no NF1 patient suffered binocular blindness at such a young age in China has ever been reported.

Lisch nodule is a specific characteristic and non-invasive diagnosis of NF1, and reported to manifest as creamy pale, hypopigmented spots on the iris in brown-eyed individuals, while hyperpigmented nodules on light iris^[2]. These asymptomatic spots are not seen at birth, and gradually increase with age. Among NF1 patients, 50% of 5-year-old, 75% of 15-year-old and 95% -100% of adults over 30-year-old could present with Lisch nodules. In our study, we found four Lisch nodules on the right eye of the mother (Figure 1D), and three on the left eye. However, these nodules are brown dome-like spots in this Chinese individual, differing from the former study. With this founding, we assume that color of the Lisch nodules do not have to be coherent with the iris color. However, further study is needed.

With the same mutation, variable clinical expressions can exist. The underlying pathogenic mechanisms and genotype-phenotype correlation are still not fully understood, remaining to be demonstrated.

In conclusion, we report two cases in one Chinese NF1 family who both harbored a novel in-frame deletion mutation of the *NF1* gene. This study may contribute to expand genetic mutation data of *NF1* gene and to some extent give insight into the genotype-phenotype relationship of *NF1*.

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Conflicts of Interest: Peng J, None; Zhang J, None; Zhang Q, None; Zhao PQ, None; Yao ZR, None.

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