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Identification of a Novel NF1 Deletion Variant in a Taiwanese Boy with Neurofibromatosis Type 1-associated Moyamoya Syndrome

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Running Title: A novel NF1 deletion variant in a Taiwanese boy with Neurofibromatosis Type 1-associated Moyamoya syndrome

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Introduction

The clinical significance of vasculopathy in patients with neurofibromatosis type 1 (NF1) has not been clearly elucidate due to its asymptomatic presentation and undetermined frequency.\(^1\) Compared with frequently affected renal arteries, NF1-associated Moyamoya syndrome (MMS), which is characterized by progressive intracranial artery narrowing and small telangiectatic vessel development, accounts for merely 0.6\% of cases.\(^2\) Nevertheless, undiagnosed MMS results in markedly high risk of ischemic and hemorrhagic stroke in young adults.\(^3\) Despite its unclear pathogenesis, a genetic association between MMS and NF1 has been confirmed.\(^3\) In this study, we report the case of 4½-year-old boy who presented with recurrent focal seizures triggered by breath-holding and was subsequently diagnosed with NF1-associated MMS linked to a novel \textit{NF1} deletion variant.
Case Report

A 4½-year-old boy was admitted to our pediatric unit. He was the first child of non-consanguineous healthy Chinese parents, and experienced frequent right-sided focal motor seizures during breath-holding triggered by crying and Todd’s paralysis since the age of 2. Despite no obvious developmental delay, he presented with inarticulate speech, impulsive behavior, excessive drooling, was easily distracted, and frequently fell when running.

A physical examination revealed blood pressure of 134/98 mmHg, respiratory rate of 28 breaths per min, heart rate of 150 beats per min, and body temperature of 36.4°C. Growth parameters were within the normal range for his age group. Nevertheless, we noticed ≥ 6 cafe-au-lait spots, sized approximately 0.5 cm in diameter, on his limbs/buttocks (Fig 1A, B, C, and D). A neurological examination revealed gait asymmetry with right leg dominance and intact muscle strength.

Serum and cerebrospinal fluid laboratory examinations showed no abnormalities; however, brain magnetic resonance imaging (MRI) identified acute ischemic infarction of the left parietal lobe. Moreover, faint T2 hyperintensities in the right pons emerged during follow-up brain MRI (Fig 1E). Subsequent brain MR angiography imaging revealed segmental narrowing of the proximal M1 segment of bilateral middle cerebral arteries (Fig 1F). Conventional electroencephalography identified left parietal sharp
waves. Next-generation sequencing (NGS) analysis of the patient’s DNA identified a heterozygous deletion of a guanine in intron 30 of the *NF1* gene (c.4110+1delG), which was previously not reported (Fig 1G). Since the clinical presentations were compatible with NF1-associated MMS, the patient was prescribed oral anticonvulsants, including levetiracetam, piracetam, and oxcarbazepine. Furthermore, left encephalo-duroarterio-synangiosis cerebral revascularization surgery was carried out. Annual neurological/ophthalmological evaluations targeting complications were performed and have been normal; furthermore, the patient has been seizure-free for 1 year.
Discussion

The high prevalence of seizures in patients with NF1 is possibly due to brain tumors and malformations during cortical development, whereas unidentified bright objects are usually considered unrelated. One suggestion is that Ras–Raf–MEK–ERK pathway hyperactivation, resulting from loss-of-function mutations in NF1 linked to dysfunctional neuronal signaling involving ion channels, may lead to a hyperexcitable brain. Additionally, pediatric NF1-related vasculopathy, particularly MMS, may also cause epilepsy-induced transient ischemic attacks and/or cerebral infarctions.

Consistent with our case's clinical presentation, patients with NF1 and MMS often display focal-onset seizures triggered by crying or intense exercise, with the seizures being associated with an exacerbation of cerebral hypoperfusion.

Aberrant neurofibromin was hypothesized to be caused by NF1 mutation, resulting in excessive vascular smooth muscle cell proliferation and impaired endothelial cell layer integrity; both seem to be involved in vasculopathy development. The identification of novel NF1 pathogenic variants via NGS has broadened our understanding of the NF1 genotype–phenotype correlation. Remarkably, the present deletion variant was located within NF1, rather than in the susceptibility gene for familial Moyamoya disease at chromosome 17q25. Despite the lack of documentation of this variant in patients with NF1-related disorder, variant c.4110+1delG located at the 3' end of NF1 exon 30, was
recently identified in a mainland Chinese individual with *café-au-lait* macules. This deletion variant, currently identified as likely pathogenic in ClinVar database, may cause RNA splicing disruption at the donor splice site of *NF1* intron 30, which will hinder normal protein expression. Unfortunately, we could not clarify the origin of the deletion because the parents refused genetic testing.
In summary, the diagnosis of NF1 in our patient was made based on *cafe-au-lait* macules and the heterozygous likely pathogenic *NF1* variant according to the revised diagnostic criteria for NF1. Notably, this case describes the occurrence of a rare neurological manifestation within a wide clinical spectrum of NF1-related genetic diseases. Notwithstanding the above, accurate recognition of the wide clinical spectrum of NF1 with advanced genetic testing technology enables early diagnosis and a better delineation of its molecular pathogenesis. **Acknowledgments**

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**Ethical approval**

This study was approved by the Ethics Committee of the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center.

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Patient consent

The patient’s parents agreed to the use of his imaging and clinical data for publication and academic research. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.
References
Fig 1. Clinical features, imaging findings, and mutational analysis of a patient with Neurofibromatosis 1-associated Moyamoya syndrome. Multiple cafe-au-lait macules were scattered on the left hand (A), left shoulder (B), left buttock (C), and right thigh (D) of the patient. Axial T1-weighted MRI imaging of the brain (E) demonstrated an unidentified bright object in the right pons (white arrow). Axial 3D time-of-flight MRA imaging (F) showed poor blood flow within the proximal M1 segment of bilateral middle cerebral arteries (white arrows). Mutational analysis by hybridization capture-based next-generation sequencing (G) revealed a c.4110 + 1delG deletion variant within NF1 at the first base downstream of the 3’ end of exon 30, and the result was validated by Sanger sequencing.

Declaration of Competing Interest

The authors have no conflict of interest relevant to this article.