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LETTER TO THE EDITOR

A novel mutation of the NKX2-1 gene: A late-onset diagnosis of benign hereditary chorea

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Benign hereditary chorea (BHC) is a rare autosomal dominant movement disorder that presents in infancy or childhood and is characterized by chorea that is either mildly progressive or nonprogressive.[1] Chorea can involve any part of the body, generally worsening in stressful conditions and disappearing during sleep. Patients may exhibit additional features, including motor developmental delays, subnormal intelligence, memory deficits, learning difficulties, dysarthria, dystonia, hypotonia, ataxia, and tremor.[1,2] Symptoms typically manifest before the age of five; however, due to overlapping clinical features such as hypotonia, ataxia, and motor developmental delays, it is often misdiagnosed as ataxic cerebral palsy prior to the onset of chorea.[1] Herein, we presented a patient diagnosed with BHC later in life.

A 24-year-old male patient was admitted with complaints of involuntary movements. The patient stated that his parents observed neurological impairment, including walking difficulties and imbalance, starting around the age of 1.5 years. The patient was born at term with normal height and weight. He was delayed compared to his peers and did not begin walking until age four. As the patient grew older, walking difficulties became more pronounced. At the age of seven, the patient developed stammering speech and sudden, involuntary, jerky movements in all extremities. In 2013, he sought evaluation at a neurology clinic for these movements. The ASO (antistreptolysin-O) titer was negative, no acanthocytes were observed in the blood, and cardiac examination yielded normal results. Brain magnetic resonance imaging (MRI) and electroencephalography were also normal. The patient was diagnosed with anxiety disorder but did not respond to treatment. The patient exhibited no dysmorphic features, had normal intelligence, and was attending university. In 2020, the patient was referred for evaluation due to worsening symptoms. Examination revealed increased deep tendon reflexes, chorea in left-sided limbs, hypotonia, truncal ataxia, and inability to tandem walk. The patient did not exhibit motor impersistence. Blood tests, including hemogram, VDRL (Venereal Disease Research Laboratory), folate, vitamin B12, ceruloplasmin, and iron levels, were normal, as were rheumatoid factor and vasculitis markers. However, thyroid stimulating hormone (TSH) was 9.17 mIU/L (reference range: 0.27-4.8), and free T4 was 1.30 ng/dL (reference range: 0.79-1.59). Urinary tests, including routine parameters and 24-h urine iron levels, were within normal ranges. A repeated 3T MRI was performed, including T1-weighted, T2-weighted, diffusion-weighted (DWI), susceptibility-weighted (SWI), fluid attenuated inversion recovery (FLAIR), gradient echo, and contrast-enhanced T1 sequences. No signal abnormalities were identified. However, we observed diffuse cerebellar atrophy of the vermis, more prominent in both hemispheres (Figure 1).

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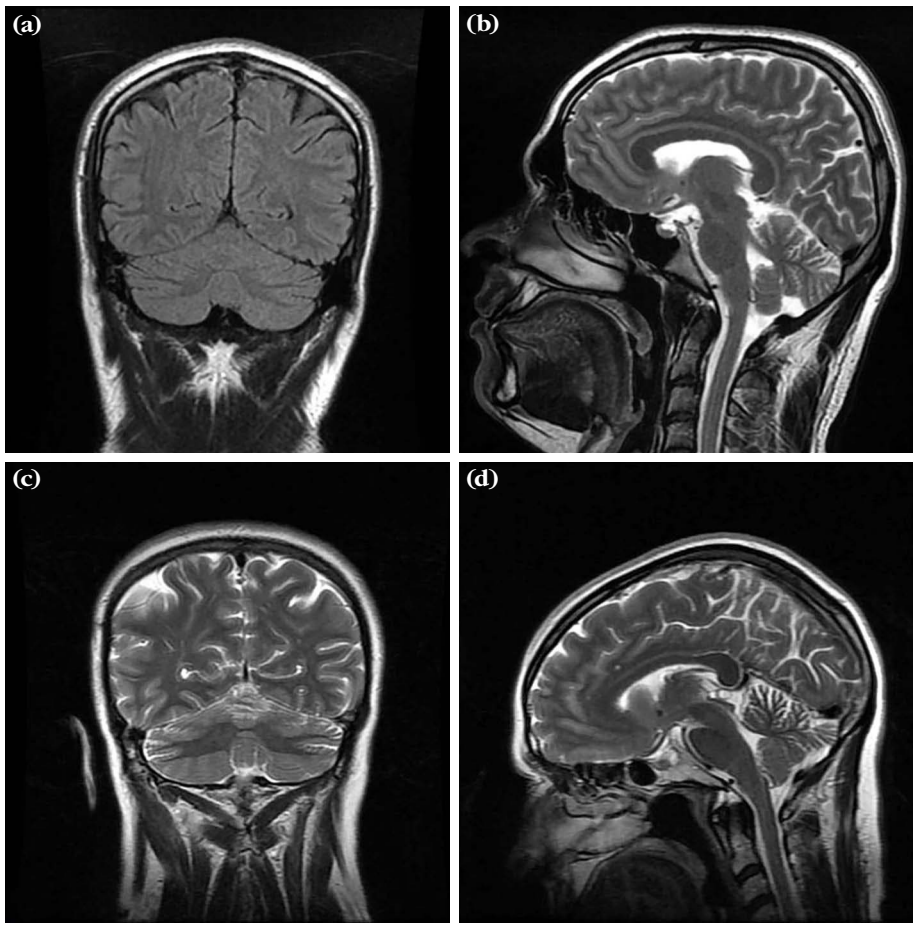

Figure 1. (a, b) The magnetic resonance imaging of the patient and **(c, d)** his mother demonstrating the cerebellar atrophy.

Upon detailed examination of the family history, the parents were not related. However, the mother presented with choreoathetoid movements in all limbs, global hypotonia, and inability to walk tandemly. Her MRI also revealed cerebellar atrophy, similar to that of the patient. Based on the patient's symptoms, developmental history, coexisting hypothyroidism, and the mother's findings, we suspected a genetically-inherited neurodegenerative disorder, possibly spinocerebellar atrophy types 1, 2, 3, 6, 7, 8, 10, 12, or 17, or dentatorubral-pallidoluysian atrophy. Clinical exome sequencing revealed a heterozygous c.200_225dup, p.(Ala76Argfs*34) frameshift mutation in DNA at location chr14:36988427, affecting the NKX2-1 gene and the NM_001079668 transcript. Screening of the ClinVar database revealed that this mutation had not been previously reported (Figure 2). This alteration was associated with benign hypotonia. According to OMIM (Online Mendelian Inheritance in Man), some patients have heterozygous mutations in NKX2-1 gene (600635), which encodes thyroid transcription factor-1 (TITF1), on chromosome 14q13. The NKX2-1 gene is also classified as "definitively pathogenic" according to the American College of Medical Genetics and Genomics guidelines.[3] The patient was diagnosed with BHC. Genetic analysis of the mother confirmed the presence of the same heterozygous frameshift mutation. At the time of this report, the patient's chorea remained nonprogressive, and he continued to demonstrate normal intelligence without receiving any treatment. Written informed consent for publication was obtained from the patient.

Chorea related to mutations in the NKX2-1 gene is a rare disorder that typically presents in infancy or early childhood; however, in the case described, the patient was diagnosed at the age of 24, significantly later than usual diagnosis time. The initial symptoms of involuntary movements,

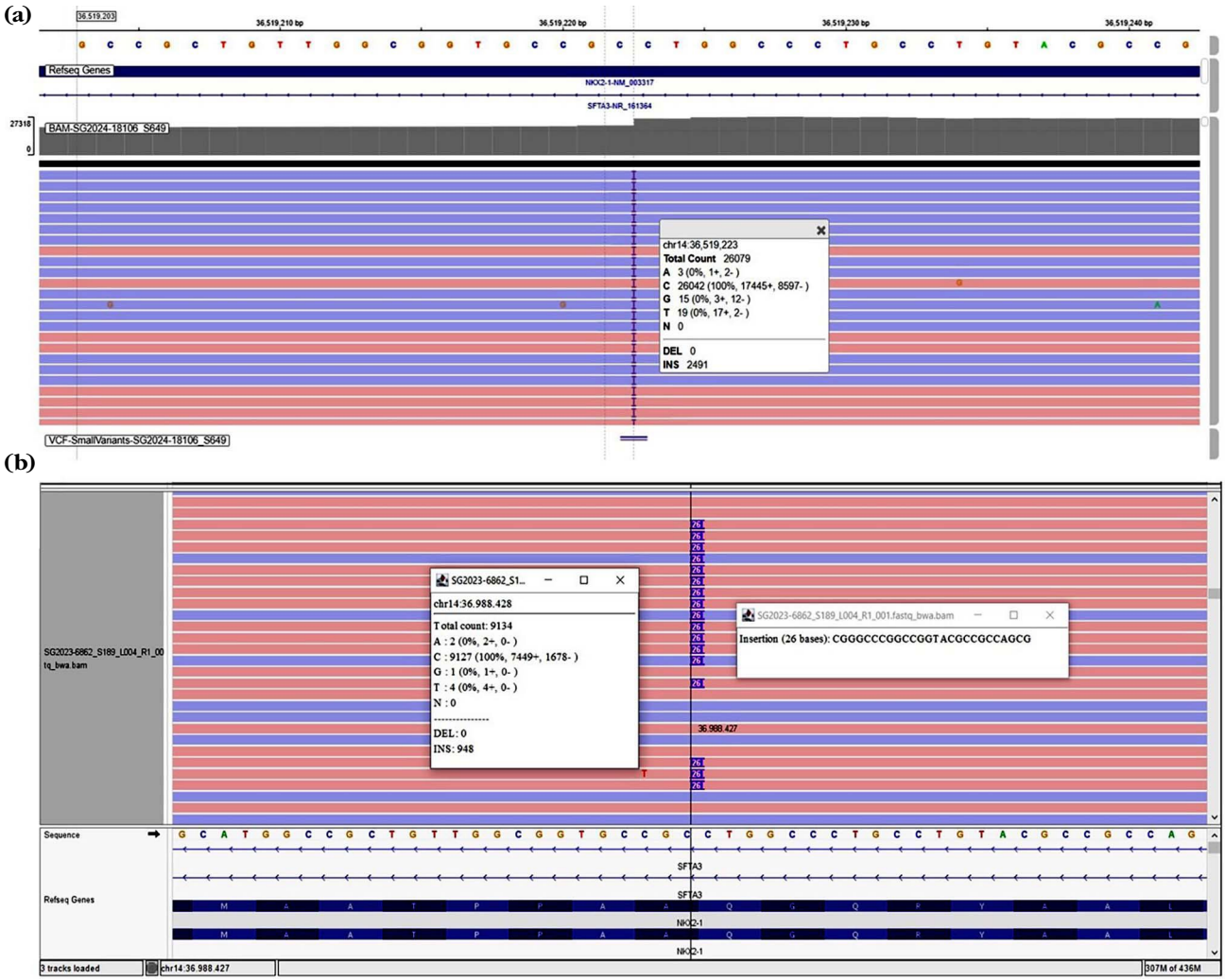

Figure 2. **(a)** Mother and **(b)** our patient Sanger sequences.

hypotonia, and delayed motor development were misattributed to an anxiety disorder, contributing to a delay in accurate diagnosis. A comprehensive review of the literature identified 13 previously reported cases, in which the patients were diagnosed after the age of five (Table 1).[4] This comparison highlights the relative scarcity of cases with delayed diagnosis.

The phenotypic spectrum of NKX2-1-related disorders demonstrates significant variability, ranging from single organ system abnormalities to combined involvement of brain, thyroid, and lungs. Neurological manifestations are often the most common, with BHC being a hallmark feature. In some cases, BHC may also be associated with respiratory distress syndrome or congenital hypothyroidism.[5] In our patient, generalized chorea, hypothyroidism, and hypotonia, along with cerebellar atrophy, were prominent features. Although MRI revealed no abnormalities; some structural anomalies were detected in 20.2% of patients, including cavum septum pellucidum, hypoplastic pallidum, agenesis of corpus callosum, hippocampal dysmorphism, Chiari type 1 malformation, and mild cerebellar atrophy.[5,6] Both our patient and his mother had cerebellar atrophy on MRI. Therefore, our findings were consistent with relevant cerebellar variations.

To date, tetrabenazine and levodopa have been reported as the most effective treatments in a limited number of patients. However, these medications produce side effects with minimal or no improvement in hyperkinetic movements. Consequently, current evidence is insufficient

TABLE 1
Diagnostic challenges and delays in NKX2-1-related disorders: A summary of clinical onset and contributing factors

Cases	Age at onset	Age at diagnosis	Delay in diagnosis	Factors contributing to diagnostic delay
Peall et al.[8] (2014) - Case 1	2 years	10 years	8 years	Diagnosis delayed due to atypical presentation and lack of genetic testing.
Balicza et al.[9] (Case 1)	2 years	46 years	44 years	Lack of genetic testing.
Balicza et al.[9] (Case 2)	1.5 years	20 years	~19 years	Underscored NKX2-1 related disorders in differential diagnosis
Doyle et al.[10] (4 cases)	Early infancy (~1 year)	10 years (mean)	~9 years	Familial inheritance obscured individual cases
Ferrara et al.[11]	7 years	25 years	13 years	Scanned after her son got the diagnosis
Gras et al.[12]	31 months (mean)	8 months to 7 years	~7 years (mean)	No delay
Hayasaka et al.[13]	Birth to 9 years	Birth (median)	~11 years (mean)	Lack of awareness about hereditary interstitial lung disease and its overlap with systemic features
Hermanns et al.[14]	Infancy to 12 years (varies)	Varied (months to years)	Up to 12 years	Lack of early molecular screening
Koht et al.[7]	Early infancy (~1 year)	~8-10 years	~7-9 years	Misdiagnosed as hereditary ataxia initially
Nakamura et al.[15]	Birth	Adolescence	~10+ years	Chorea often misattributed to other causes
Narumi et al.[16]	Birth to neonatal period	Varied (months to years)	~10+ years	Phenotypic variability including thyroid dysgenesis without systemic symptoms
Uematsu et al.[17]	Birth (~early infancy)	Adolescence (~13 years)	~10-12 years	Coreoathetosis often attributed to developmental delays
Veneziano et al.[18]	Infancy (~1 year)	Late childhood (~8-9 years)	~7-8 years	Newly identified de novo mutation in TITF1/NKX2-1 leading to misdiagnosis of movement disorders
Our case	1.5 years	24 years	22.5 years	Symptoms were misattributed to anxiety disorden.

TITF1: Thyroid transcription factor-1.

to establish standardized treatment guidelines.[7] Optimal management includes physical activity, physiotherapy, and multidisciplinary support in educational and occupational life, along with regular monitoring and treatment of lung and thyroid function as necessary.[6,7]

In conclusion, clinicians should consider BHC in differential diagnosis of ataxia, chorea, and hypotonia even in adult life. This case highlights diagnostic challenges in atypical presentations of BHC, underscoring importance of genetic counselling in movement disorders.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Designed and directed the project: B.C.A., G.K.; Performed the genetic analyses: S.C.; Wrote the article: B.C.A., G.K., S.C.

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