A RARE HOMOZYGOUS VARIANT OF THE *NKX6-2* GENE IN ASSOCIATION WITH PROFOUND INTELLECTUAL DISABILITY

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This is a study of five children with profound intellectual disability, spastic quadriplegia, and nystagmus in two distinct families. Whole exome sequencing (WES) identified a homozygous c.234dup variant in the NKX6-2 gene relating to Spastic ataxia 8 with hypomyelinating leukodystrophy - the underlying cause of severe neurodevelopmental impairment in both families. The study contributed additional data on NKX6-2 variants in Vietnamese patients with intellectual disabilities and explored the genotype-phenotype correlation. Furthermore, it emphasized the importance of early genetic testing in children presenting with developmental delay, spastic quadriplegia, and unexplained nystagmus, especially when brain MRI findings suggested hypomyelinating leukodystrophy. This approach will provide a critical basis for diagnosis, patient management, and genetic counseling.

Keywords: *NKX6-2* gene, leucodystrophy hypomyelinating, spastic ataxia-8, intellectual disability.

I. INTRODUCTION

Hypomyelinating leukodystrophies (HLD) are a heterogeneous group of genetic disorders resulting from defects in the formation of the myelin sheath in the central nervous system (CNS), characterized by global developmental delay, hypotonia, spasticity, and intellectual disability of varying degrees.[1-3] Myelination is a complex but crucial process for the development and function of the CNS in vertebrates. This process is tightly regulated by a complex network of transcription factors and microRNAs that modulate the downstream genes and metabolic pathways through interconnected feedback loops.[4-6] Mature postmitotic oligodendrocytes, myelin-generating glial cells, are responsible for the axonal myelin ensheathment in the CNS.[7] Inherited or acquired defects in oligodendrocytes, its precursors, and the myelination regulatory network can lead to abnormal myelination (dysmyelination) or insufficient myelination (hypomyelination).[6] The clinical features of HLD and MRI findings are often diverse and overlapping among subtypes, sharing characteristics with other causes of white matter degeneration. Therefore, extensive genetic testing is required for precise diagnosis.[8] Advances in next-generation sequencing have significantly improved the diagnostic process.[1,2] Hypomyelination can result from dysfunctions in pathways involved in the production or maintenance of the myelin sheath. These include mutations in genes encoding myelin proteins (*PLP1*), enzymes involved in myelin protein translation (*POLR3A, POLR3B, POLR1C*), and proteins mediating astrocyte-oligodendrocyte interactions (*GJC2*).[9]

Recently, homozyguos or heterozyguous variants in *NKX6-2* gene have been reported

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in individuals with spastic ataxia type 8 (SPAX8), hypomyelinating leukodystrophy.[1,9-14] The *NKX6-2* gene (OMIM: 605955) is located on chromosome 10; which is 2,969 base pairs in size, and consists of three exons. It encodes NK6 homeobox 2, a transcription factor belonging to the homeobox family, which plays a critical role in CNS development during embryogenesis.[15] This protein is essential for maintaining myelin production and regulates the expression of genes involved in myelin synthesis and assembly, including proteolipid protein (PLP), myelin basic protein (MBP), cyclic nucleotide phosphodiesterase (CNP), myelin-associated glycoprotein (MAG), and myelin glycoprotein.[4,16,17] *NKX6-2* is also expressed in the testes and pancreatic cells.[17]

We report two families with multiple affected members with profound intellectual disability, carrying pathogenic homozyguos variants in *NKX6-2* gene, identified through whole exome sequencing (WES) and confirmed by Sanger sequencing for familial segregation. Our study aims to provide additional data on *NKX6-2* variants in the Vietnamese population and analyze genotype-phenotype correlations. Additionally, it highlights the importance of early genetic testing in children presenting with cerebral palsy, spastic quadriplegia, and unexplained nystagmus, particularly when brain MRI findings suggest hypomyelinating leukodystrophy. Early genetic diagnosis can improve disease management and genetic counseling for affected families.

II. CASE REPORTS

1. Clinical manifestation

Case 1: Two siblings in a family (III.13 & III.15, Figure 1), presenting with profound intellectual disability, were brought to the Center of Clinical Genetics and Genomics, Hanoi Medical University Hospital, for evaluation and genetic counseling. Noticably, their mother was pregnant the fourth time at 14 weeks of gestation.

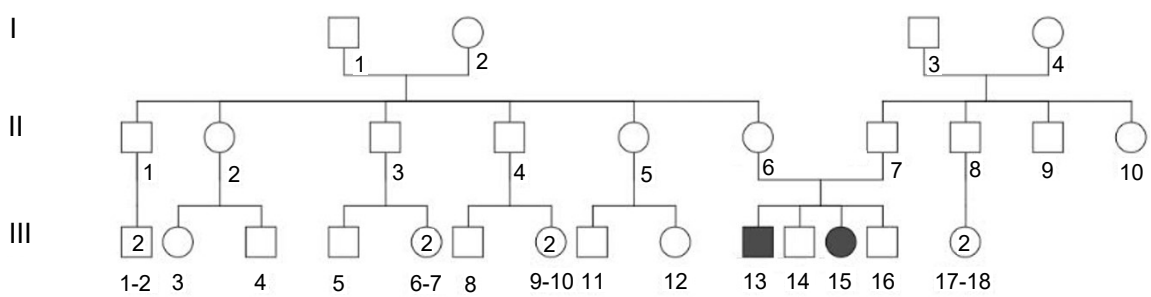

Figure 1. Family pedigree in Case 1

The younger sister (III.15, Figure 1): An 11-year-old girl with normal pregnancy and perinatal history. At one month old, she exhibited nystagmus and abnormal eyes movement. By four months, she exhibited head lag and had not achieved any motor or cognitive milestones. She was examined at the National Children's Hospital and diagnosed with spastic cerebral palsy while no MRI scan was performed. Despite undergoing physical therapy, her condition did not improve. She was brought to the Center of Clinical Genetics and Genomics at the age of 10, presenting with loss of ambulation- unable to walk or roll over, with muscle atrophy in all four limbs, lower limb rigidity, joint contractures, clubfoot, clenched hands, and an absence of speech despite auditory responses. Her head circumference was 40cm, height 90cm,

and weight 8 kg (< 1st percentile). No distinct dysmorphic facial features were observed. She experienced daytime episodes of generalized tonic seizures while awake. Older brother (III.13): A 16-year-old boy with the disease onset and clinical presentation similar to his younger sister. Additionally, he had scoliosis. Both siblings were unable to chew solid food but could swallow milk, porridge, and soft rice. They lacked bowel and bladder control and were prone to recurrentillnesses, including fevers and upper respiratory tract infections.

Case 2: Three children in a family, all presenting with profound intellectual disability, were brought to the Center of Clinical Genetics and Genomics, Hanoi Medical University Hospital for evaluation and genetic counseling. This consultation took place during a preconception counseling session for the parents before their fourth pregnancy.

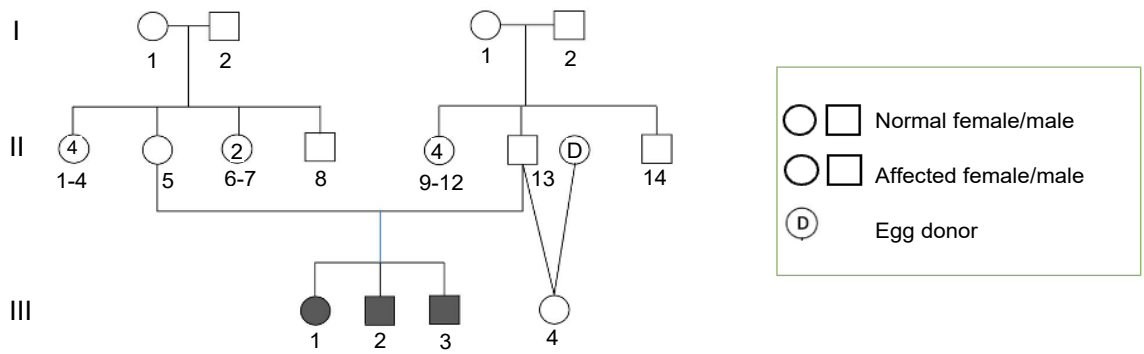

Figure 2. Family pedigree in Case 2

The youngest child (III.3, Figure 2) is a 7-year-old boy who had no remarkably finding during pregnancy and perinatal period. Aroundone month of age, he began showing signs of nystagmus and abnormal eyes movements. By six months old, he had head lag, hypotonia then developed spastic quadriplegia. He was examined at the National Children's Hospital and diagnosed with spastic cerebral palsy. Metabolic disorder screening revealed no abnormality and MRI scan was not conducted. Despite undergoing physical therapy and acupuncture, no significant improvement was observed. At the age of five, he was brought to the Center of Clinical Genetics and Genomics, presenting with profound cognitive and motor impairment - unable to speak, unable to walk or roll over, with muscle dystrophy in all four limbs, lower limb rigidity, joint contractures, clubfoot, and clenched hands. He responded to auditory stimuli but was nonverbal. His height was 80 cm, and his weight was 8kg (< 1st percentile). No distinct dysmorphic facial features were observed. The 12-year-old brother (III.2) and 14-year-old sister (III.1) also presented a similar disease onset and clinical presentation. All three children were unable to chew solid food but could swallow milk and porridge. They had no bowel or bladder control. In early childhood (under five years old), they frequently suffered from fever and upper respiratory infections, though that had improved with age.

Table 1 summarized clinical characteristics of two children with profound intellectual disability among five affeted children in two families.

Table 1. Summary of clinical manifestation

of two probands from two families

	Proband III.15 (Fig. 1)	Proband III.3 (Fig. 2)
Case	1	2
Gender	Female	Male
Age	11 years old	7 years old
Pregnancy and perinatal history	Normal	Normal
Consanguinity	(-)	(-)
Family history	Older brother (III.13) : Similar onset and clinical manifestation, with additional scoliosis	Older sister (III.1) and older brother (III.2): Similar onset and clinical manifestation
Onset age	1 month	1 month
Diagnosis before genetic testing	Cerebral palsy	Cerebral palsy
Diagnosis of genetic cause	10 years old	5 years old
Psychomotor development	Profound developmental delay	Profound developmental delay
Facial dysmorphy	(-)	(-)
Growth parameters	Head circumfrance 40cm, Height: 90cm, Weight: 8kg	Height: 80cm, Weight 8kg
Ophthalmological findings	Nystagmus, abnormal eyes movement	Nystagmus, abnormal eyes movement
Skeletal findings	Joint spasticity of the limbs, clenched hands, clubfoot, inability to chew, only able to swallow liquid or pureed food.	Muscle atrophy in all four limbs, joint contractures, clenched hands, clubfoot.
Other findings	Recurrent inflammation Responsive to auditory stimuli Generalized tonic seizures Lack bowel and bladder control.	Recurrent inflammation Responsive to auditory stimuli Lack bowel and bladder control.
Brain MRI	Not done	Not done

2. Genetic results

Case 1: The affected sister was subjected to whole exome sequencing (WES) (III.15, arrow, Fig 3) The results identified a homozygous variant in the *NKX6-2* gene (NM_177400.3:c.234dup). Following the identification of this variant, first-degree relatives including the parents (II.6 and II.7), the affected brother (III.13), and the healthy brother (III.14) were subjected to Sanger sequencing to confirm the inheritance

pattern and provide additional segregation data for variant classification. Additionally, the mother, who was 18 weeks pregnant, underwent amniocentesis and simultaneous Sanger sequencing on the amniotic fluid sample to avoid late-stage amniocentesis as the pregnancy progressed.

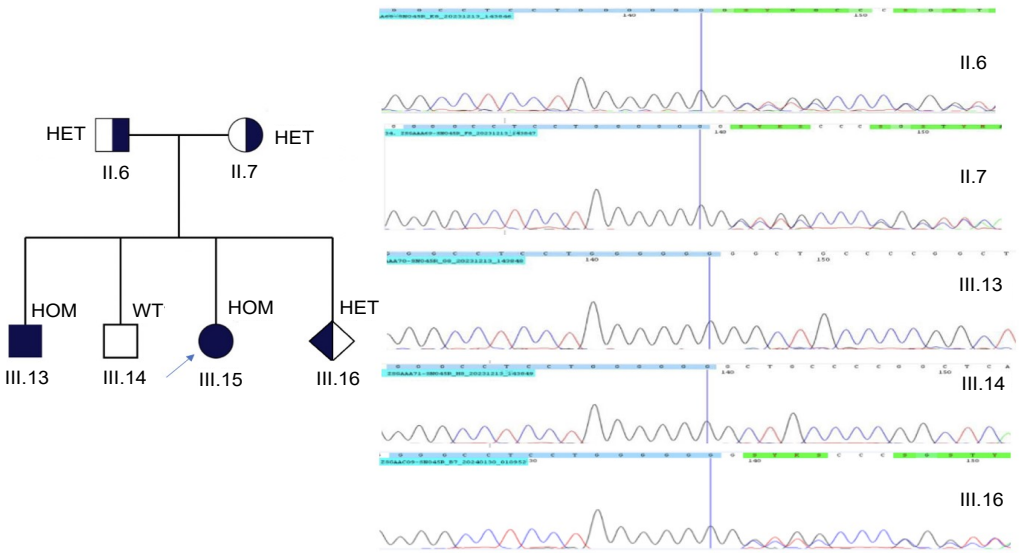

Figure 3. Alleles segregation in the family in case 1 (left) and Sanger sequencing results (right) *(Note: HET: Heterozygous; HOM: Homozygous; WT: Wild type)*

The findings showed that the father (II.6), mother (II.7), and the amniotic fluid sample (III.16) carried the heterozygous c.234dup (p.Leu79CysfsTer109) variant, while the healthy older brother (III.14) did not carry the variant. After birth, proband III.16 is now a 9-month old girl with no disease manifestation and has achieved age-appropriate neurodevelopmental milestones.

Case 2: The youngest affected son (III.3, arrow, Fig. 4) was subjected to whole exome sequencing (WES). The results detected a homozygous c.234dup variant in the *NKX6-2* gene. Following this discovery, first-degree relatives including the parents, the affected older brother (III.1), and the affected older sister (III.2) underwent direct Sanger sequencing to confirm the inheritance pattern and provide additional segregation data for variant classification.

The results showed that the affected older sister (III.1) and affected older brother (III.2) carried the homozygous c.234dup variant in the NKX6-2 gene, inherited from their parents (II.5 and II.13), who were both heterozygous carriers of the variant. The couple was counseled on preimplantation genetic diagnosis (PGD) or prenatal diagnosis (PND) for future pregnancies. However, based on the family's preference, they opted for in vitro fertilization (IVF) with egg donation for their fourth pregnancy.

The sanger sequcing performed on the amniotic fluid sample at 17 weeks of gestation (III.4) identified a heterozygous c.234dup variant in the NKX6-2 gene. After birth, the child (a 5-month-old boy) has shown no disease symptom and is achieving age-appropriate neurodevelopmental milestones, including rolling over and early vocalization.

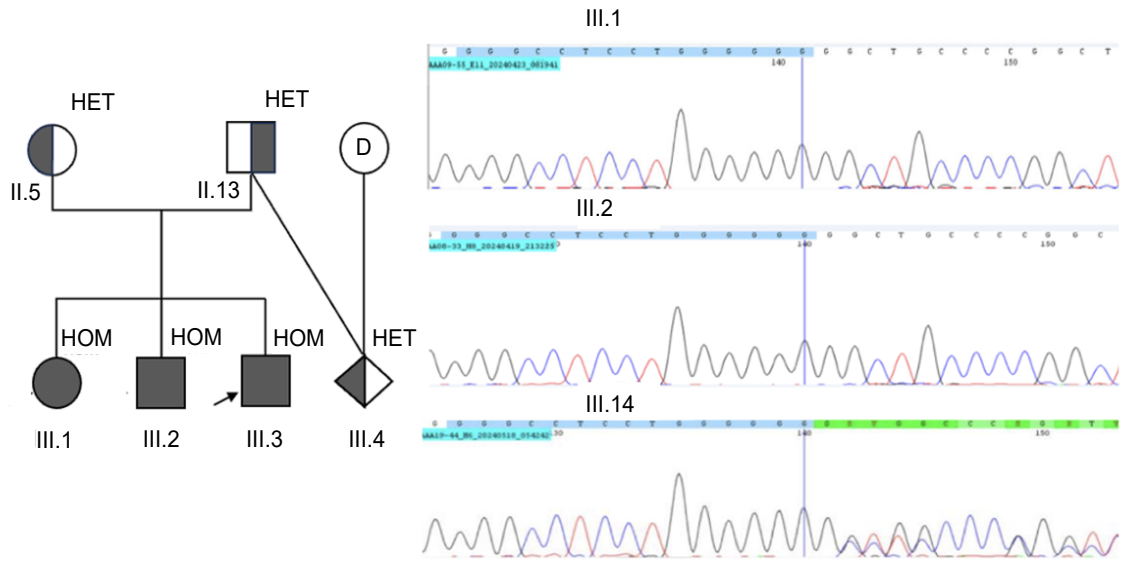

Figure 4. Alleles segregation in the family in case 2 (left) and Sanger sequencing results (right) *(Note: HET: Heterozygous; HOM: Homozygous)*

3. Variants interpretation

The NM_177400.3:c.234dup (p.Leu79AlafsTer381) variant is a nucleotide duplication in exon 1/3 of the NKX6-2 gene. This results in a frameshift mutation, leading to a premature stop codon at position 381, causing a loss-of-function (LOF) effect. This variant is classified as Pathogenic/Likely Pathogenic based on clinical variant data from the U.S. National Institutes of Health (ClinVar), with two reports classified as likely pathogenic and one report as pathogenic. One of these reports was linked to spastic ataxia 8 with hypomyelinating leukodystrophy.

According to the American College of Medical Genetics and Genomics (ACMG), Association for Molecular Pathology (AMP), and ClinGen SVI guidelines, the variant is classified as Pathogenic based on the following criteria:

PVS1: Loss-of-function (LOF) variant in the NKX6-2 gene, which has been associated with disease (13 other LOF variants have been identified in affected individuals).

PM3: The variant is in trans with a known pathogenic variant in an autosomal recessive disorder.

PM2: The variant has a low allele frequency in the general population (f = 0.00003 in the gnomAD database).

PP4: The clinical phenotype and family history are consistent with the disease associated with this variant.

PP1: The variant is co-segreggation multiple family members.

III. DISCUSSION

Hypomyelinating leukodystrophy is a genetically heterogeneous disorder that affects the central nervous system and presents with a broad phenotypic spectrum. Diagnosis and classification are often challenging due to non-specific clinical features and MRI findings. To overcome these challenges, we performed whole-exome sequencing (WES) on one affected individual from each family, followed by Sanger sequencing validation in other affected siblings and first-degree relatives. This approach confirmed segregation

of the genotype and identified the disease-causing variant. Our genetic analysis revealed that the homozygous c.234dup variant in the *NKX6-2* **gene, inherite**d from heterozygous parents, was the underlying cause of disease in all five affected children across the two families. Following this discovery, we compared the genotype-phenotype correlation with previous reports and proposed a diagnostic approach for severe/profound neurodevelopmental delay with spastic quadriplegia, pyramidal signs, and cerebellar involvement in children with suspected genetic etiology.

Spastic Ataxia Type 8 (SPAX8) is a hypomyelinating disorder caused by homozygous or compound heterozygous variants in the *NKX6-2* gene. The disease manifests in two main forms: the severe perinatal-onset form, which presents with early-onset nystagmus (1–3 months of age), hypotonia, and progressive developmental delay, followed by spastic quadriplegia, joint contractures, pyramidal tract degeneration, cerebellar, and brainstem involvement by late infancy.[10-14,18] The later-onset form, in which children achieve early neurodevelopmental milestones within the first year of life but later develop progressive spastic ataxia, pyramidal tract dysfunction, cerebral palsy-like symptoms, and neurodevelopmental delay.[19] To date, 40 individuals from 24 families of diverse ethnic backgrounds, primarily from the Middle East, have been diagnosed with NKX6-2 variants through whole-exome sequencing (WES) or whole-genome sequencing (WGS). Shaymaa Shurrab et al. analyzed these cases and concluded that homozygous loss-of-function (LOF) variants, including truncating mutations and missense mutations affecting the homeodomain region, are associated with earlier and more severe disease onset.[19] The disease mechanism is primarily thought to involve nonsense-mediated mRNA decay (NMD). However, recent findings by Pedro Ferreira-Peralta et al. suggest an additional protein misfolding mechanism contributing to SPAX8 pathology.[20] In our two clinical cases, we identified a frameshift variant in exon 1 of NKX6-2 (c.234dup), leading to a premature stop codon after 109 codons, confirming loss-of-function is the causing pathogenicity of the severe form of SPAX8.

All five children from the two families reported in our clinical cases exhibited early-onset symptoms shortly after birth, with nystagmus and abnormal eye movements appearing between 1 - 3 months of age. However, families only sought medical evaluation when the children were 4 - 6 months old, as they had delayed head control and inability to roll over. The disease then progressed to profound neurodevelopmental delay, inability to walk or speak, and spastic quadriplegia. Shaymaa Shurrab et al. previously reported a patient carrying the homozygous c.234delG (p.Leu79CysfsX109) variant in *NKX6-2*, with onset at 3 months, presenting spastic quadriplegia, profoound developmental delay, nystagmus, strabismus, and vision impairment.[19] MRI findings in that patient showed marked diffuse hypomyelination involving the cerebral hemispheres, brainstem and cerebellum, diffuse thinning of the corpus callosum, slender brainstem and small vermis. The clinical presentation and disease progression in our cases align with previous literature, which associates early-onset disease with severe neurodevelopmental impairment due to defective CNS myelination.[9,18,19,21]

The term spastic ataxia refers to the overlap between cerebellar ataxia and spastic paraplegia. José Luiz Pedroso et al. proposed a diagnostic approach for spastic

ataxia based on age of onset, family history, and MRI abnormalities. In cases of early-onset spastic ataxia or MRI-detected white matter abnormalities, leukodystrophy should be considered as a primary differential diagnosis (Figure 5).

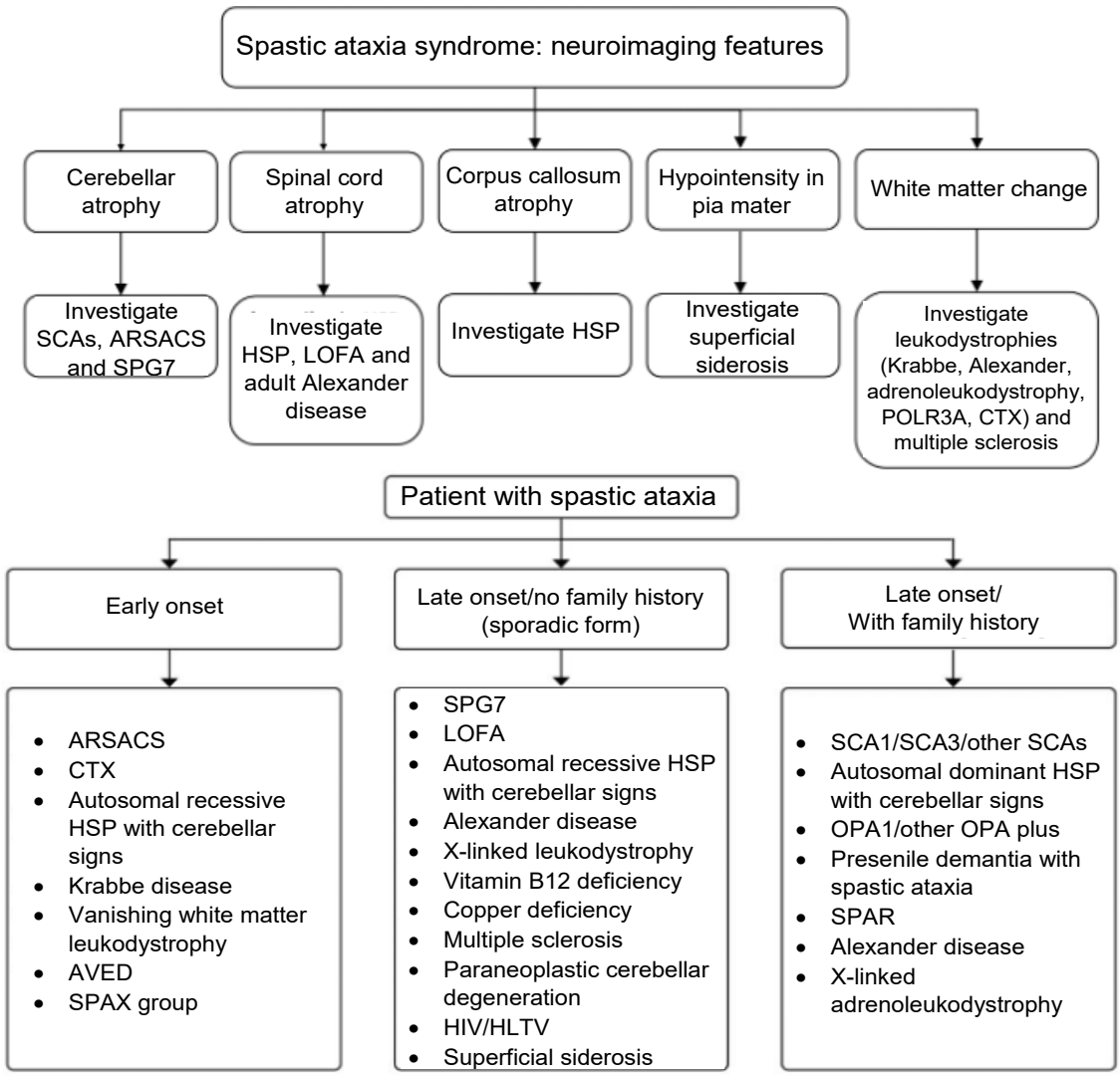

Figure 5. Diagnosis approach in spastic ataxia based on neuroimaging features and onset age/ family history[22]

All five affected children in the initial examination process were diagnosed with spastic cerebral palsy but were not prescribed MRI scans or genetic testing at the onset of the disease. While spastic cerebral palsy is diagnosed based on clinical features and is considered an acquired disorder, recent studies have increasingly demonstrated the genetic causes of cerebral palsy.[23] MRI abnormalities are not among the diagnostic criteria for cerebral palsy; however, 80% of children with spastic cerebral palsy present abnormalities on brain MRI scans, which help determine the underlying mechanism and cause of the

disease.[24,25] International consensus has recognized the importance of brain MRI in diagnosing cerebral palsy, recommending it as the first diagnostic step after taking a medical history and conducting neurological examinations.[26] With the development of broad-spectrum genetic testing, the genetic origins of cerebral palsy have become an increasingly discussed topic.[23] Specifically, in the two families reported in our study, it was challenging to differentiate between the clinical features of early-onset spastic ataxia and spastic cerebral palsy due to overlapping symptoms: progressive hypotonia rapidly evolving into spastic quadriplegia, impaired motor abilities, signs of pyramidal tract damage, hyperreflexia, cerebellar involvement (such as nystagmus), and profound psychomotor developmental delay. The pregnancy and delivery history of all affected children were normal, without risk factors such as infections or respiratory distress. Unfortunately, in both families, the diagnosis of a genetic cause was significantly delayed, only being conducted after two to three children were affected, all of whom had lost the ability to perform daily activities, frequently suffered from recurrent respiratory infections, and faced difficulties in digestion and feeding due to their inability to chew. This imposed a considerable burden on both the affected families and the healthcare system.

Therefore, we want to emphasize the importance of genetic testing in children exhibiting signs of spastic cerebral palsy, particularly in those without risk factors for acquired cerebral palsy during pregnancy and labor, and with MRI abnormalities suggestive of hypomyelinating leukodystrophy. This approach aids in disease management and, more importantly, enables genetic counseling and prenatal diagnosis for future pregnancies within affected families.

IV. CONCLUSION

Spastic ataxia 8 caused by variants in the *NKX6-2* gene is a rare form ofhypomyelinating leukodystrophy, the early onset type is characterized by neonatal-onset nystagmus, lower limb hypotonia, regression, spastic quadriplegia, and profound global psychomotor developmental delay. The rarity of the disease, the heterogeneous clinical presentation, and the diverse genetic causes of other forms of hypomyelinating leukodystrophy pose significant challenges in establishing a diagnosis based solely on phenotype, conventional laboratory tests, and routine imaging studies.

Therefore, we recommend whole-exome sequencing (WES) or whole-genome sequencing (WGS) for children presenting with clinical features and brain MRI findings suggestive of hypomyelinating leukodystrophy. Our case series report also contributes to the growing body of evidence in the medical literature regarding spastic ataxia type 8 caused by a homozygous variant in the NKX6-2 gene, leading to profound psychomotor developmental delay in Vietnamese pediatric patients.

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