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CASE REPORT

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Hypomyelination and Congenital Cataract: Identification of a Novel likely pathogenic c.414+1G>A in *FAM126A* gene Variant

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Abstract

It is key to expand the differential diagnosis and consider possible genetic etiologies on a patient with congenital cataracts associated with clinical features, such as leukodystrophy or polyneuropathy.

KEYWORDS

FAM126A gene, Hypomyelination and congenital cataract, white matter disorder

1 | INTRODUCTION

We report a patient with an uncommon presentation of Hypomyelination and Congenital Cataract and a novel likely pathogenic variant (c.414+1G>A) in *FAM126A* gene. Patient presented early delayed psychomotor development, bilateral congenital cataracts, and hypomyelination in the brain magnetic resonance. Analysis of *FAM126A* gene detected the c.414+1G>A homozygous likely pathogenic variant.

Hypomyelination and congenital cataract (HCC) is a rare autosomal recessive white matter disorder.[1] HCC has a typical triad of bilateral congenital cataract, neurological impairment with peripheral neuropathy, and a typical hypomyelination pattern on brain magnetic resonance image (MRI).[2] It affects the myelin in the central and peripheral nervous system,[3] and it is caused by mutations in the *FAM126A* gene on chromosome 7p15. These mutations cause a deficiency of FAM126A membrane protein, also known as hyccin.[4,5] Although FAM126A protein function is not completely clear, it has been related to the phosphatidylinositol 4-phosphate (PI4P) production in oligodendrocytes and to the myelination process in both the central and peripheral nervous system.[6,7]

HCC has characteristic clinical and MRI findings. Usually, all patients have normal prenatal and perinatal histories[5] and present with bilateral congenital cataracts identified at birth or in the first months of life. There are two types of presentations: the classical and the uncommon presentations. In the first one, patients have normal psychomotor development in the first year of life, followed by a slowly progressive neurologic impairment, peripheral neuropathy, loss of the ability to walk, and mild-to-moderate cognitive impairment. Patients can also present with cerebellar signs and truncal hypotonia.[8]

The uncommon presentation is characterized by either early-onset severe variant (<1 year of life) or late-onset mild variant (> 2 years of life).[3] The MRI has a pattern consistent with hypomyelination, with a hyperintense signal of supratentorial white matter on T2-weighted images, associated with preserving both cortical and deep gray matter structures and isointense to mild hypointense signal on T1-weighted images.[1]

2 | CASE REPORT

2.1 | Clinical report

The proband is a male child, born from parents who originated from an island in Chile, with surname isonymy between the great grandfather of the father and great grandmother of the mother of the patient. The patient has a younger 5-year-old healthy brother and a 3-month-old sister diagnosed with bilateral congenital cataracts and normal development. There is no other relevant family history, with an unremarkable pregnancy history. The proband was born at term, normal anthropometry, and a normal perinatal period. At 3 months of age, bilateral congenital cataracts were identified, and the patient underwent surgery at 4 months of age. The patient developed a central hypotonic syndrome, and according to the mother's report, he showed a delayed psychomotor development, achieving cephalic control at 6 months old, sat unsupported at 1 year old, never achieving independent gait, and using a wheelchair for transfer. The developmental assessment showed a delay in language with apparently normal social communication skills. The Pediatric Neurology Department received the patient at the age of 15 years old. Physical examination demonstrated a moderate intellectual disability and severe scoliosis. He did not present dysmorphisms; he had normal ocular movements, divergent strabismus, and multidirectional nystagmus. He had axial and low limbs hypotonia with normal osteotendinous reflexes in upper extremities and absent in inferior extremities, active movement against gravity of four limbs, and leg wasting. The patient had no cerebellar signs, and he did not present gait, using a wheelchair for transfer. An MRI was performed, demonstrating a diffuse abnormal white matter, including internal capsule with high intensity in frontal regions in T2-weighted sequences with hypointensity in T1-weighted sequences; enlargement of ventricles and subarachnoidal space; and diffuse thinning of the corpus callosum, without compromise of the cerebellum Figure 1. This pattern was compatible with an extensive supratentorial hypomyelination with myelin destruction

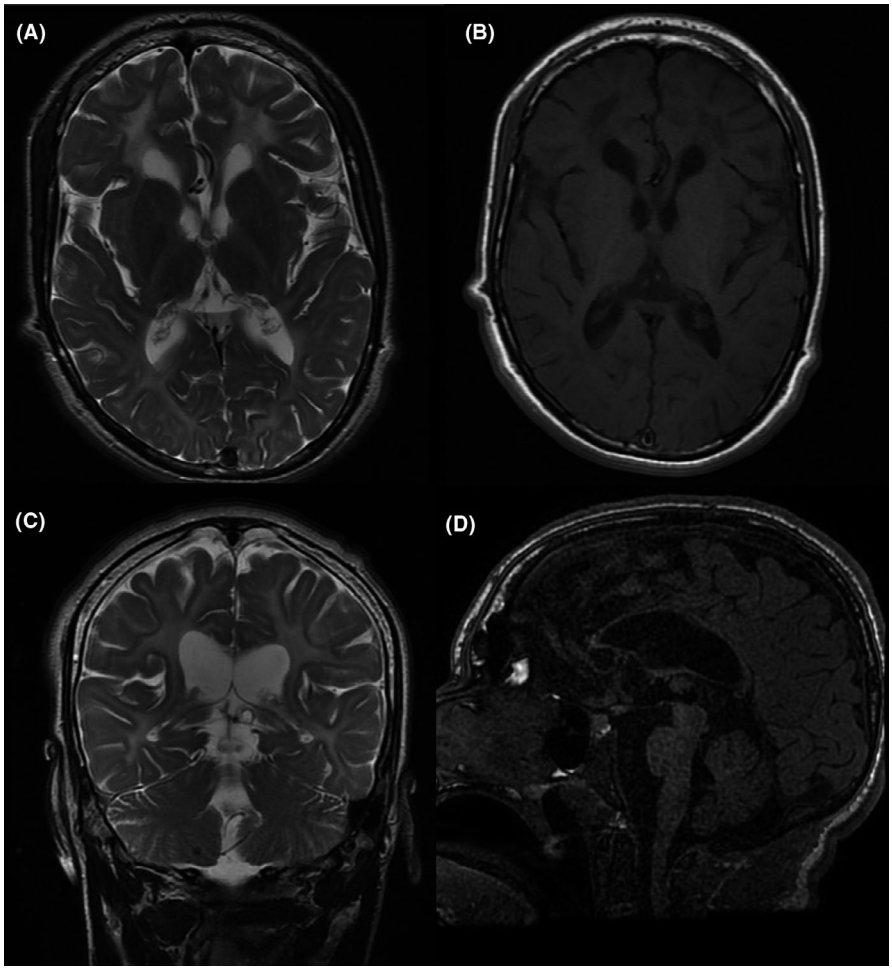

FIGURE 1 (A) Axial T2-weighted sequence: diffuse supratentorial hyperintense white matter affecting internal capsule consistent with hypomyelination. (B) Axial T1 weighted sequence: iso and hypointense white matter. (C) Coronal T2-weighted sequence: supratentorial hyperintense white matter, enlarged ventricles and subarachnoid space. (D) Sagittal T1-weighted sequence: diffuse thinning of the corpus callosum

and cerebral atrophy. The medullar MRI presented normal white matter. An electromyography and nerve conduction were also performed, demonstrating a chronic sensorimotor demyelinating polyneuropathy with secondary axonal loss. The patient had a normal electroencephalogram and normal cardiac findings.

2.2 | Molecular genetics

Next-generation sequencing (NGS) analysis of *FAM126A* gene was performed to confirm the clinical diagnosis. An intronic homozygous likely pathogenic c.414+1G>A variant was detected in intron 5. Carrier status of the parents and homozygous status in the proband were confirmed by Sanger sequencing Figure 2. Afterward, screening of *FAM126A* for c.414+1G>A was performed for both siblings: the unaffected brother and the cataract affected sister. The Sanger sequencing showed a carrier status of the 5-year-old healthy brother and homozygous status in the 3-month-old affected sister.

This variant has not been previously reported but is located at the same nucleotide position of the c.414+1G>T pathogenic mutation already reported[6] and registered in Human Gene Mutation Database (HGMD).

3 | DISCUSSION

We report a case of HCC with bilateral congenital cataracts, peripheral neuropathy, progressive neurological impairment, and typical MRI pattern with hypomyelination. The presented case had an early-onset severe variant as described in previous research[3] with developmental delay in the first months of life, early hypotonia, without being able to acquire independent gait, and with wheelchair dependency. The MRI demonstrated primary myelin deficiency (hypomyelination), and secondary neurodegenerative changes, with cerebral atrophy (enlargement of ventricles and subarachnoid space) as it is was mentioned by Rossi et al[1]

The genetic analyses showed a likely pathogenic homozygous variant (c.414+1G>A) in *FAM126A* gene in both the proband and affected sister. Also, we found the same variant in heterozygous state in both unaffected parents and healthy brother. Thus, these findings are highly suggestive that the presence of this variant in a homozygous state is causative of the autosomal recessive HCC disorder in the proband.

As it was reported previously, a different homozygous mutation (c.414+1G>T) located in the same intronic position would cause a splicing error and the complete lack of FAM126A protein.[6] The c.414+1G>A mutation is located at the first nucleotide of the intron, which is always

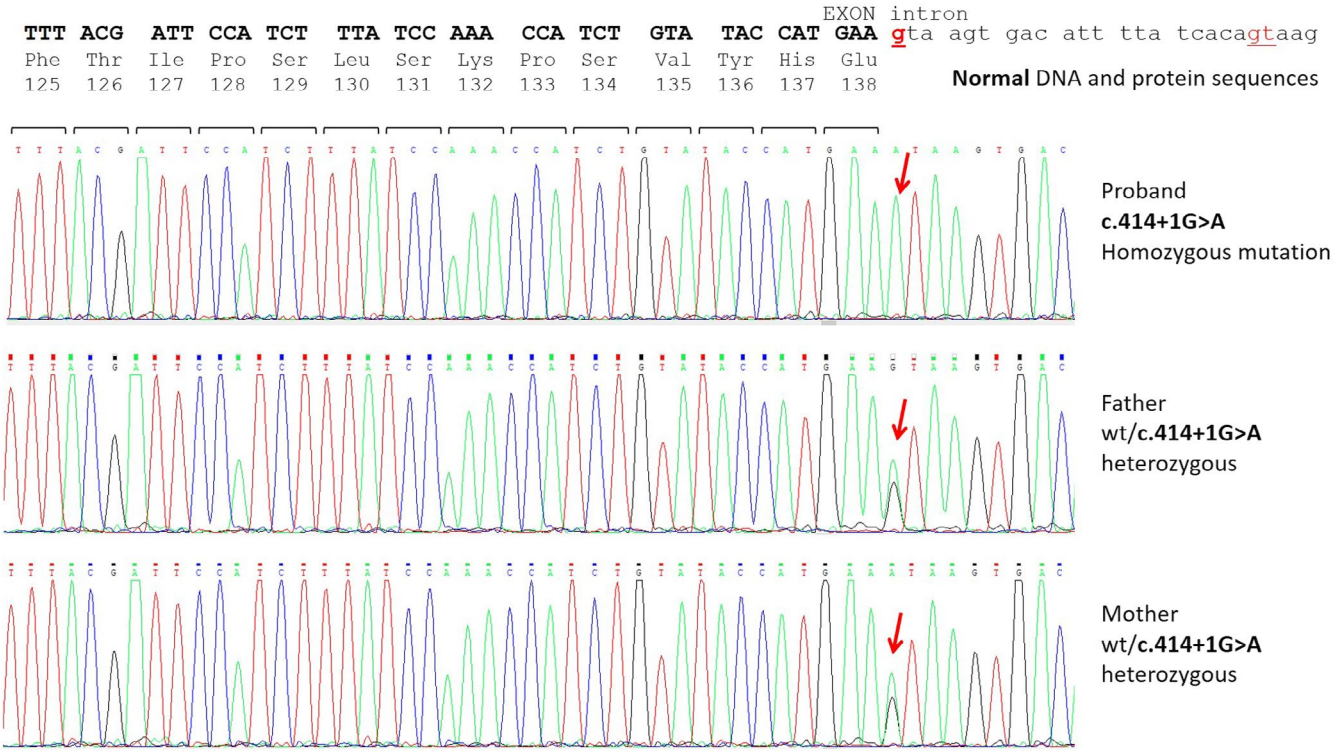

FIGURE 2 Sanger sequence confirmation of the homozygous c.414+1G>T variant in the proband and heterozygous variant in both parents. The normal DNA and protein sequences and codon positions are presented on the top. In red are shown the G nucleotide of the normal and cryptic donor splicing sites. Below, the electropherograms of the proband and both parents are presented. The sequence in the proband shows homozygosity and in the parents shows heterozygosity with overlapping sequences due to the c.414+1G>A mutation (red arrow)

conserved in GT-AG rule introns, and therefore, it eliminates the splice donor site. Consequently, it is very likely that the G to A nucleotide change reported in the Chilean family described here has the same effect as the G to T nucleotide reported by Zara et al.[6,] causing an mRNA splice error. This splice error would lead to the use of a cryptic splice site downstream in intron 5, resulting in the insertion of a 20 bp intronic segment into the FAM126A mRNA and causing a frameshift and a premature stop codon. The premature termination codon would result in nonsense-mediated decay (NMD) of the mRNA with the lack of protein in the proband. NMD is a mechanism that controls the quality of mRNA, accelerating the degradation of abnormal mRNAs harboring a premature termination codon (PTC), preventing the generation and accumulation of possibly toxic truncated proteins.[9] The clinical severity of the proband can be likely explained due to the mutation described that caused absence of the hyccin protein.

Since the proband and his family lived on a small island, there is surname isonymy in the family, and both parents present the same variant; endogamy, and the possibility that this could be a founder mutation cannot be ruled out.

Congenital cataracts are an early feature of this disease. Usually, in a newborn or infant with this feature, one of the differential diagnosis is a congenital infection (TORCH). Still, if the clinical course is progressive or deteriorating, or in the presence of leukodystrophy, we should consider other possible etiologies, among them, metabolic or genetic etiologies.[10,11]

4 | CONCLUSION

We report a likely pathogenic variant in the *FAM126A* gene, highly probable responsible for the phenotype of HCC in a patient with uncommon presentation. We want to highlight the importance of considering and studying genetic etiologies in patients with congenital cataracts that present with other progressive clinical features. In our case, the presence of hypomyelination in the MRI and polyneuropathy associated with congenital cataracts were key elements to suspect this diagnosis and performed a direct *FAM126A* gene study.

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CONFLICT OF INTEREST

None of the authors declare any conflict of interest.

AUTHOR CONTRIBUTIONS

MT: contributed as the attending physician of the patient and provided a critical review of the manuscript. FB: contributed to the draft and submission of the manuscript. SW and JC: contributed to the clinical management of the patient. CR and FC: contributed to the genetic study process. LH: contributed to the genetic study process and draft of the manuscript.

ETHICAL CONSIDERATIONS

Both parents agreed to the use of clinical information and photographs for purposes of this publication. Informed consent was obtained written from legally authorized representatives. This study was approved by the Ethics Committee of the Faculty of Medicine of the Universidad de Chile and adhered to the tenets of the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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