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Original Article - Case Study

Late-onset cerebellar ataxia in an adult with a novel mutation in the *CLN5* gene

Raashda A. Sulaiman[1,2,], Salma Majid Wakil[3], Saeed Boholega[4]*

[1]Department of Medical Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[2]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[3]Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[4]Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

* *Corresponding author*: Dr. Raashda A. Sulaiman, Department of Medical Genetics, MBC: 75, King Faisal Specialist Hospital and Research Centre, PO Box No: 3354, Riyadh, 11211, Saudi Arabia; Phone: +966-11-4424988; Fax: +966-11-4424126; Email: rsulaiman@kfshrc.edu.sa

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ABSTRACT

Neuronal ceroid lipofuscinosis (NCL) is a neurodegenerative disorder which mostly presents in early life and is associated with a premature death. Here, we report a 50-year-old Saudi male who presented with cerebellar ataxia and whole exome sequencing identified a previously undescribed, homozygous mutation in the *CLN5* gene (c.562T>C; p.Phe188Leu). This mutation was predicted to be pathogenic based on bioinformatics tools scoring; PolyPhen-2 (1) and SIFT (0.0). He did not have a visual impairment, cortical atrophy or cognitive decline, which were reported in previous adult cases associated with *CLN5* mutation. This case, therefore, further expands the molecular and clinical phenotype associated with *CLN5* mutation. It also highlights the role of next-generation sequencing analysis in providing early insights and diagnosis of rare hereditary disorders.

Keywords

Neuronal ceroid lipofuscinosis, adult-onset, cerebellar ataxia, whole-exome sequencing, *CLN5* mutation.

Abbreviations

Neuronal ceroid lipofuscinosis (NCL), endoplasmic reticulum (ER), Magnetic resonance imaging (MRI), ceroid lipofuscinosis neuronal protein 5 (CLN5), Whole exome sequencing (WES).

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) is a genetically heterogeneous group of neuro-degenerative disorders, characterized by the intra-lysosomal accumulation of auto-fluorescent, lipopigments in neural and peripheral tissues[1]. Mutations in at least 14 genes (*CLN1-CLN14*) have been identified to cause various forms of NCL[2]. The *CLN5* gene located on chromosome 13q22 encodes for ceroid lipofuscinosis neuronal protein 5 (CLN5), which is a soluble lysosomal protein. Its precise function remains unknown[3]. A recent study reveals the possible role of CLN5 in mitochondrial energy homeostasis and activation of mitophagy[4]. It has been shown that mutant CLN5 protein is retained in the endoplasmic reticulum (ER) and it does not reach the lysosome, indicating that *CLN5* mutations affect ER-lysosomal trafficking[3,5]. CLN5 disorder is inherited in an autosomal recessive pattern. Bi-allelic mutations in *CLN5* result in a phenotype characterized by motor impairment, visual loss, seizures and cognitive regression[3,6]. The onset of symptoms is either in childhood or up to early

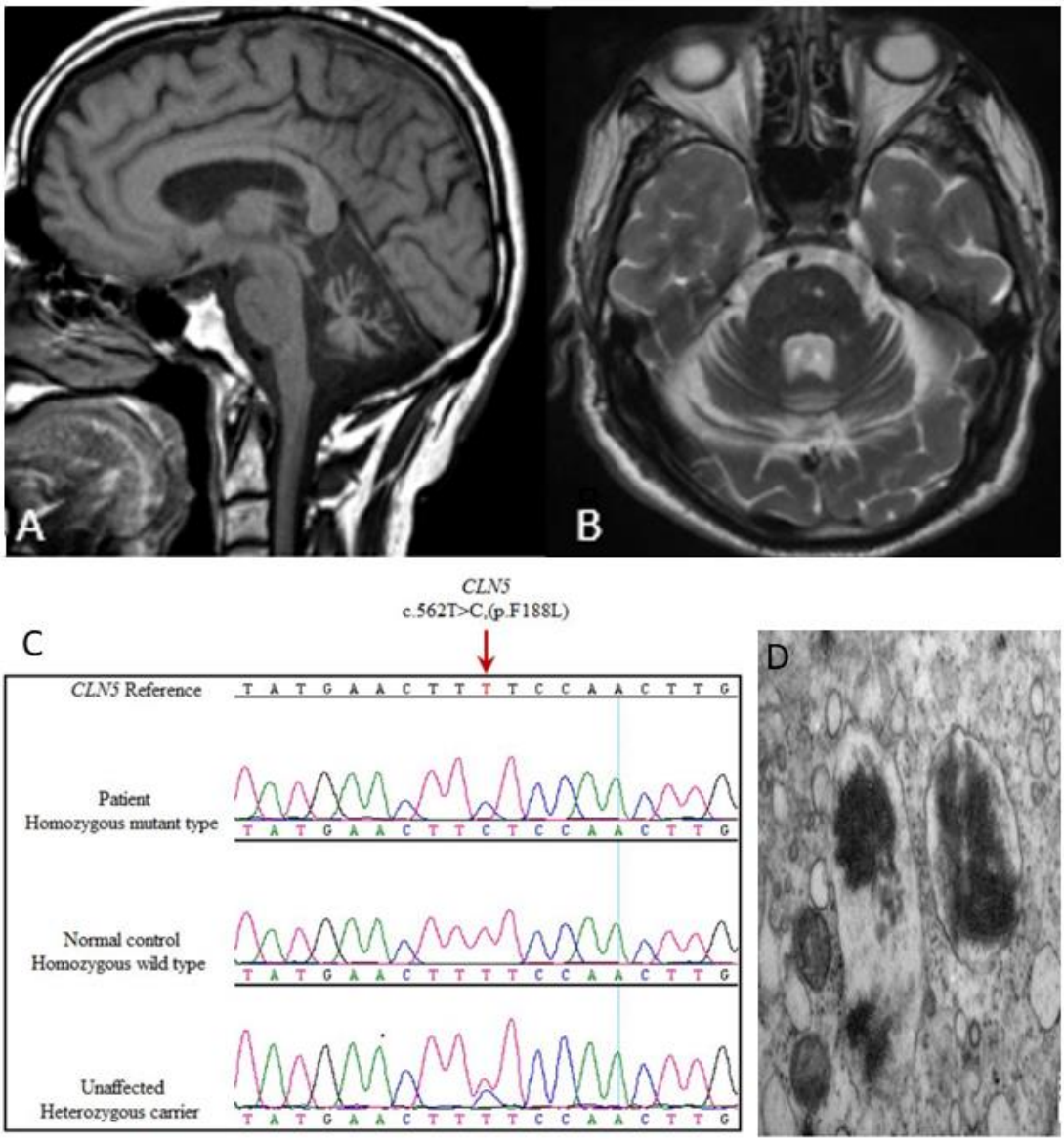

Figure 1. Radiological, molecular and lymphocyte abnormalities in a 50-year-old Saudi male with cerebellar ataxia and a homozygous mutation in the CLN5 gene (c.562T>C; p.Phe188Leu)
(A) Sagittal and (B) axial views of MRI brain showing cerebellar atrophy; (C) Sanger sequence chromatograms of CLN5 showing the normal control, unaffected heterozygous carrier, and affected patient with a homozygous mutation. The arrow indicates a single base T > C transition in exon 3 of CLN5; (D) Electron microscopy of peripheral lymphocytes showing focal collections of intra-lysosomal storage material.

adulthood (4-17 years). Here, we report a case in which the cerebellar ataxia associated with *CLN5* mutation, developed in late-adult life.

CASE REPORT

A 50-year-old Saudi male was referred to the neurology clinic with a history of progressive unsteady gait for ten years and slurred speech for six years. He did not have seizures or visual impairment. His parents were first cousins, and there was no history of similar illness in the family. On examination, he had ataxia, dysarthria, bilateral horizontal nystagmus, dysmetria and dysdiadokokinesis. He had no muscle atrophy, or weakness and sensations were intact. His vision was normal, and there was no cognitive decline. Magnetic resonance imaging (MRI) of the brain

showed cerebellar atrophy, most significantly involving the vermis (Figure 1A, B). There was no cerebral atrophy. Whole exome sequencing (WES) revealed a novel pathogenic homozygous missense mutation in *CLN5* (c.562T>C; p.Phe188Leu), which was confirmed by Sanger sequencing (Figure 1C). Subsequent electron microscopic examination of peripheral lymphocytes showed focal collections of storage material with the ultrastructure of fingerprint bodies (Figure 1D). Family screening could not be performed, since his parents were deceased and healthy siblings refused to be tested.

DISCUSSION

NCL associated with *CLN5* mutation was initially reported in Finnish population, in Europe[7]. Later, patients from a diverse ethnic background were diagnosed to have CLN5-related disease[3,8,9]. It mainly presents in younger age, varying from infancy to the second decade of life. There is only one previous report of two Italian siblings presenting in the mid-50s[6]. We presume that specific *CLN5* mutations have a less severe impact on the CLN5 protein, initially preserving its residual function. It, therefore, takes longer to cause significant damage, resulting in late onset of the disease.

Using WES, we identified a novel homozygous mutation in exon 3 of the *CLN5* gene; a single base T > C transition that caused a substitution of phenylalanine to leucine at codon 188 (c.562T>C; p. Phe188Leu). The c.562T nucleotide is highly conserved throughout evolution, as is the corresponding amino acid phenylalanine. The p.Phe188Leu mutation was predicted to be pathogenic by using two bio-informatics tools, such as PolyPhen-2 (http://genetics.bwh.harvard.edu /pph2/) and SIFT (http://sift.bii.a-star.edu.sg/), which give a score representing the probability that an amino acid substitution is damaging. PolyPhen-2 revealed a score of 1.0 (range - 0.0: tolerated; 1.0: deleterious) and SIFT a score of 0.0 (range- 1.0: tolerated; 0.0: deleterious). This mutation was not present in the 1,000 Genome project database, 1,000 Arab exomes and 700 Saudi exomes databases. Demonstration of characteristic membrane-bound inclusion bodies in lymphocytes further supported the diagnosis of NCL[10,11].

In the previous report, Italian siblings presented with cerebellar ataxia, mild cognitive, visual impairment, and cortical atrophy associated with *CLN5* mutation[6]. Our patient had cerebellar ataxia but no cognitive loss, cortical atrophy or visual disturbance. Hence, this case further expands the spectrum of neurological phenotypes associated with CLN5-related adult-onset NCL.

Saudi Arabia has one of the highest incidence rates of autosomal recessive diseases, and NCL constitutes 5% of the neurodegenerative disorders seen in children[12]. This is the first report of cerebellar ataxia associated with *CLN5* mutation, presenting in a middle-aged Saudi adult. It emphasizes the need for considering genetic testing even when there is no family history of a similar disorder. Molecular diagnosis also facilitates preventive reproductive measures in such cases where no curative treatment is available.

CONCLUSION

Adult-onset cerebellar ataxia associated with *CLN5* mutation is a rare disease. This case expands the neurological phenotype of CLN5 disease and suggests that it should be considered in the differential diagnosis of late-onset cerebellar ataxia even when there are no visual failure, seizures or cognitive decline. WES is not only facilitating the early diagnosis of rare diseases with novel mutations, but is also expanding the spectrum of associated phenotype.

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Conflict of Interest

The authors declare no conflict of interest.

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