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"UNVEILING THE GENETIC OVERLAP: FIG4 MUTATIONS LINKING PARKINSON DISEASE, CHARCOT-MARIE-TOOTH DISEASE 4J, AND CEREBELLAR ATAXIA"

Neurology

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ABSTRACT

Parkinson's disease (PD) and Charcot-Marie-Tooth disease (CMT) are neurodegenerative disorders typically distinct in their genetic and clinical manifestations. However, recent studies reveal overlapping genetic etiologies, particularly through mutations in the FIG4 gene, known for its role in cellular phosphoinositide metabolism. This report details the case of a 40-year-old male with a unique clinical profile characterized by progressive Parkinsonian features, hereditary sensorimotor neuropathy, and cerebellar ataxia, all associated with a novel homozygous mutation in FIG4. The patient presented with gait disturbances, rigidity, dysarthria, and distal muscle wasting, alongside neurophysiological findings indicative of a sensorimotor demyelinating neuropathy. Genetic analysis identified the FIG4 mutation, implicating this gene in a broader neurodegenerative spectrum. This case highlights the phenotypic diversity associated with FIG4 mutations and underscores the importance of genetic analysis in atypical presentations. The findings extend our understanding of FIG4's role in complex neurodegenerative conditions and support its potential impact on central and peripheral nervous system pathologies, offering insights for future diagnostic and therapeutic approaches.

KEYWORDS

CMT 4J,Genetic Parkinson, FIG 4

INTRODUCTION:

Parkinson's disease is a neurodegenerative disorder first clinically characterized by James Parkinson in 1817. It is recognized as a complex condition influenced by both genetic and environmental factors. The prevalence of Parkinson's disease is approximately 0.3% in the general population and rises to 1% among individuals aged over 60 years. The incidence ranges from 8 to 18 cases per 100,000 person-years. Although primarily a disease of the elderly, it has also been observed in younger individuals, referred to as young-onset Parkinson's disease (diagnosed before the age of 40).

While Parkinson's disease is predominantly sporadic, around 5-10% of cases report a positive family history, exhibiting distinct autosomal recessive or dominant inheritance patterns. Although numerous genes have been implicated in familial Parkinson's disease, only a select few—specifically SNCA, LRRK2, VPS35, PRKN, PINK1, GBA, and DJ-1—have been robustly associated with typical cases. Advances in genetic testing have led to the identification of novel susceptibility genes linked to Parkinson's disease. Studies by Quadri et al. (2018), Guo et al. (2018), Park et al. (2014), Harrison et al. (2009), and Lee et al. (2019) have identified various novel genes and mutations contributing to early-onset Parkinson's disease, both in familial and sporadic contexts.

Charcot-Marie-Tooth disease (CMT) is a clinically and genetically heterogeneous group of disorders primarily characterized by distal sensorimotor neuropathy, with an incidence of approximately 1 in 2,500 individuals. CMT4J represents a rare subtype of CMT, resulting from mutations in the FIG4 gene.

The FIG4 gene, which encodes the human phosphoinositide 5-phosphatase, is located on chromosome 6q21 and belongs to the SAC domain-containing protein family. It is highly expressed in the brain, endocrine tissues, skin, and respiratory systems. FIG4 plays a critical role in neuronal development and is essential for preventing neurodegeneration through endolysosomal trafficking.

Mutations in the FIG4 gene have been associated with a spectrum of syndromes, including Yunis-Varon syndrome, familial epilepsy with polymicrogyria syndrome, CMT4J, and ALS11. However, to date, no reports in the literature have identified FIG4 mutations with a homozygous autosomal recessive inheritance pattern in the context of Parkinson's disease.

Case Report:

A 40-year-old male with no known comorbidities presented with a primary complaint of the following symptoms: 1) Slowness in daily activities for 8 years, 2) Stiffness in both lower limbs for 8 years, 3) Unsteadiness of gait for 7.5 years, 4) Speech disturbances for 7 years, and 5) Weakness in both feet and hands for 7 years.

Upon detailed history-taking, it was noted that the patient was normal 8 years ago. His wife observed a gradual onset of slowness in his daily activities, accompanied by a hypophonic voice. The stiffness in both lower limbs began insidiously 8 years ago and has progressively worsened, without associated muscle thinning, twitching, toe tripping, or falls.

Approximately 7.5 years ago, the patient developed unsteadiness while walking, characterized by swaying to the right side. This symptom also had an insidious onset and has progressively worsened, although he has not experienced falls or specific aggravating factors, such as difficulties in the dark or with closed eyes. There are no accompanying sensations of spinning, aural fullness, hearing loss, nausea, or vomiting, and there are no issues with tremors while reaching for objects.

One year later, the patient's wife noted increasing difficulty with tasks such as mixing foods and opening jars, leading to food spillage between his fingers, though he did not smear food on his face while eating. He also reported difficulty in fitting his feet into footwear and maintaining grip on slippers, although he did not have issues getting up from a squatting position, climbing stairs, or combing his hair.

The patient does not report any sensory deficits, cranial nerve dysfunction, or autonomic symptoms. Additionally, there is a positive family history of similar illnesses.

Examination Findings

The patient was conscious and oriented, exhibiting dysarthria but maintaining normal language abilities and intact memory.

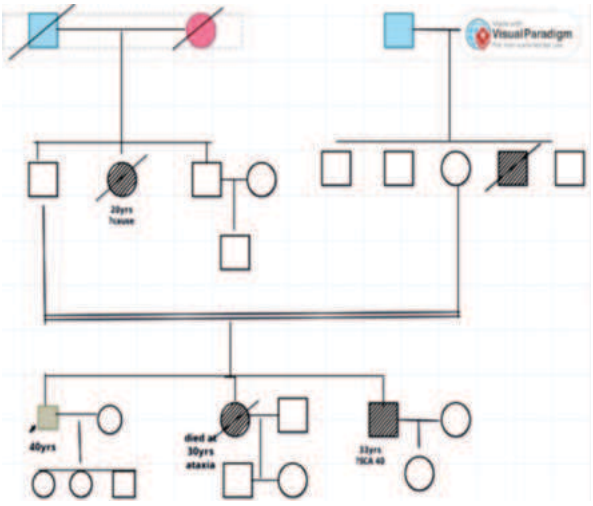
Cranial Nerve Examination:

- Slow saccades
- Broken pursuits
- Normal fundoscopic examination

Spinomotor Examination:

- Wasting of the small muscles in the hands and feet, characterized by an inverted champagne bottle appearance of both legs and pes cavus deformity.
- Rigidity noted in all four limbs.
- Muscle strength assessment revealed 4/5 power in the mid and distal groups of both upper and lower limbs, while the proximal muscle groups demonstrated normal strength.
- Deep tendon reflexes were hypoactive, with bilateral plantar flexor responses.

Pedigree:



Sensory Examination:
- Graded sensory loss extending to the lower third of the legs.

Extrapyramidal Examination:
- Reduced blink rate and an expressionless face.
- Decreased amplitude of rapid alternating movements.
- Reduced arm swing while walking.
- Cogwheel rigidity observed in both wrist joints.

Cerebellar Examination:
- Axial ataxia more pronounced than appendicular ataxia.
- Positive Romberg test.
- No nystagmus observed.

Gait Assessment:
- The patient demonstrated a short, shuffling gait.

Electrophysiological Examinations
Nerve Conduction Study (NCS) of All Four Limbs:
- Sensorimotor Demyelinating pattern of neuropathy with prolonged F wave minimum latency

Electroencephalogram (EEG):
- Diffuse background slowing with a frequency of 6-7 Hz.

MRI Brain:
- Diffuse cerebral and cerebellar atrophy(Vermis >hemisphere)

Basic Blood Investigations:
- Complete Blood Count (CBC), Random Blood Sugar (RBS), Renal Function Tests (RFT), and Liver Function Tests (LFT) were all within normal limits.
- HIV 1 & 2, HBsAg, Anti-HCV, and VDRL were negative.

Genetic Analysis:
- **SCA PANEL:** Negative
- Whole exome sequencing was conducted.

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
FIG4 (NM_014845.6)	Exon 21	c.3421_3424del p.Asp908Alafs*30 [49X/49X]	Homozygous	Likely pathogenic	Charcot-Marie-Tooth disease, type 4J	Autosomal recessive

DISCUSSION:
The clinical findings in this case point toward a complex neurological disorder characterized by hereditary sensorimotor demyelinating neuropathy, Parkinsonian features, and cerebellar ataxia. The identification of a novel homozygous mutation in the FIG4 gene, coupled with a positive family history of similar illnesses in the patient's siblings, supports the hypothesis of a genetic etiology for this presentation.

FIG4 mutations have been previously associated with various neurodegenerative conditions, including Charcot-Marie-Tooth disease and other syndromes characterized by motor and sensory deficits. The combination of sensorimotor neuropathy and extrapyramidal symptoms, such as rigidity and bradykinesia, suggests a possible overlap between the features of CMT and Parkinson's disease. The presence of cerebellar ataxia further complicates the clinical picture, indicating potential involvement of both peripheral and central nervous systems.

This case underscores the importance of genetic analysis in elucidating the underlying causes of such complex presentations, especially in the context of familial occurrences. The discovery of a FIG4 mutation not only aids in confirming the diagnosis but also has implications for genetic counseling and potential future therapeutic approaches.

Overall, this patient exemplifies the intricate interplay between hereditary neuropathies and neurodegenerative disorders, highlighting the need for a multidisciplinary approach in diagnosis and management. Further research into the functional consequences of FIG4 mutations may provide deeper insights into the mechanisms of neurodegeneration and inform strategies for intervention.

Homozygous Inheritance And Prevalence:
Homozygous mutations in FIG4 are relatively rare but have been documented in a subset of patients with hereditary neuropathies and neurodegenerative disorders. While the precise prevalence of FIG4 mutations in the broader spectrum of neurodegenerative diseases remains unclear, several case reports and series have noted associations with conditions such as CMT4J, ALS11, and occasionally features resembling Parkinson's disease and ataxia. The rarity of these mutations emphasizes the need for genetic testing in atypical presentations.

Multiple Phenotypes In A Single Case: Patients with FIG4 mutations can present with multiple phenotypes due to the gene's role in various cellular processes affecting both peripheral and central nervous systems. Phenotypic variability can include:
1. **Hereditary Sensorimotor Neuropathy:** Characterized by progressive weakness and sensory loss.
2. **Extrapyramidal Symptoms:** Such as rigidity, bradykinesia, and tremors, resembling Parkinson's disease.
3. **Cerebellar Ataxia:** Manifesting as balance difficulties and coordination problems.

This phenotypic diversity suggests that FIG4 mutations can lead to a spectrum of neurological manifestations, possibly due to differences in genetic background, environmental factors, or the specific nature of the mutation.

CONCLUSION
This case underscores the complex interplay between hereditary neuropathies and neurodegenerative disorders, particularly within the context of FIG4 mutations. The identification of a novel homozygous FIG4 mutation in a patient exhibiting Parkinsonian features, Charcot-Marie-Tooth disease (CMT)-like neuropathy, and cerebellar ataxia provides new insights into the gene's role in a broader neurodegenerative spectrum. FIG4 mutations may contribute to various neurological phenotypes, spanning both central and peripheral nervous system involvement. This case highlights the diagnostic value of genetic analysis in patients with overlapping and atypical neurological symptoms, guiding personalized treatment strategies and informing genetic counseling. Future research should focus on elucidating FIG4's molecular mechanisms in neurodegeneration, which could pave the way for novel therapeutic approaches addressing the multifaceted impacts of this mutation.

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