Open Journal of
Clinical & Medical
Case Reports

Volume 11 (2025)
Issue 07

Case Report ISSN: 2379-1039

Deciphering the genetic link between familial hypobetalipoproteinemia and neuromuscular disorder: A clinical case report

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Abstract

We present a case of a 21-year-old male patient who showed symptoms of both Familial hypobetalipoproteinemia and neuromuscular abnormalities linked to a mutation (c.7564C>T) in the APOB gene in addition to several other mutations identified that are potentially related to neuromuscular disorders. Familial hypobetalipoproteinemia is characterized by low levels of lipids in the blood due to genetic mutations affecting lipoprotein pathways, including the APOB gene. Although muscular atrophy symptoms are less commonly associated with APOB mutations, they were observed in this case. This report emphasizes the importance of recognizing the potential overlap of these two different disorders and other mutations we see in our patients and provides valuable information for clinicians who may encounter similar cases. A 21-year-old male presented to a primary care clinic with a chief complaint of muscle weakness, particularly in his upper extremities, which he has noticed over the past year. He reports difficulty performing pushups and other physical activities required by his military duties. There is no significant family history of neuromuscular disorders. He reports no allergies and is not on any regular medications. His physical training routine is rigorous, which brought his muscle weakness to his attention. This study presents the first reported instance of multiple genetic mutations correlating with a specific set of neuromuscular symptoms. This case presents evidence suggesting that lipid metabolism disorders may contribute to secondary muscular complications, potentially through mechanisms such as lipid accumulation, oxidative stress, and resultant muscle damage. This underscores the complexity of genetic disorders and the need for further research to clarify the implications of these mutations. The impact of these findings underlines the complexity of genetic interactions in neuromuscular disorders and the necessity for more extensive research to elucidate the connection between these mutations and FHBL. Further studies will be crucial in determining these variants' pathogenicity and clinical relevance, highlighting the importance of ongoing genetic screening in patients with unexplained neuromuscular symptoms.

Introduction

Familial Hypobetalipoproteinemia (FHBL) is a rare genetic metabolic disorder characterized by decreased levels of lipids in the blood, often leading to a reduced risk of cardiovascular diseases [1]. Several genetic mutations have been linked with FHBL, which involves the essential proteins controlling lipid metabolism: Low-Density Lipoprotein Receptor (LDL-R), Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), and Apolipoprotein B (APOB) genes [2]. Gain-of-function in the PCSK9 gene, such as the p.S127R mutation, increases Low-Density Lipoprotein (LDL) cholesterol levels.

This occurs because PCSK9 regulates the degradation of LDL receptors, and this mutation results in fewer LDL receptors on the liver surface, reducing the clearance of LDL from the blood stream [3]. Other LDL receptor mutations result in glycine substituting for tryptophan at position 66, leading to a defective receptor that cannot properly bind LDL particles [4]. The APOB gene, which encodes apolipoprotein B, a primary component of LDL, is among the key players in this process [2]. Several mutations in the APOB gene can result in changes in APOB lipoprotein structure, which causes abnormal lipoprotein profiles, leading to hypolipidemia and decreased LDL cholesterol levels [5]. On the other hand, neuromuscular disorders are genetic conditions that can also be associated with metabolic disorders, and several reports have shown an association between FHBL and neuromuscular disorders. For example, FHBL is noted that some patients with APOB mutation exhibit symptoms of muscle weakness alongside their lipid abnormalities [6]. Another study observed that patients with APOB mutations not only presented with hypobetalipoproteinemia but also reported instances of muscle weakness [7]. These findings suggest a possible association between aberrant apolipoprotein B forms and different mutations that impact muscle function. This case report describes a patient with symptoms associated with FHBL and neuromuscular disorder. The coexistence of FHBL and other muscular dystrophy in a single patient has not been previously reported in the literature, making this case unique and clinically significant. Our patient presents with symptoms consistent with both FHBL and muscular disorder, including low cholesterol levels, fat malabsorption, proximal myopathy, and electromyography findings suggestive of neuromuscular pathology. We explore the link between these conditions using a combined approach of clinical and biochemical observations and genetic testing. Understanding these associations could provide potential therapeutic avenues for managing lipid and neuromuscular disorders, offering hope for improved clinical outcomes. We invite the reviewers to consider the implications of this case, which not only advances the scientific understanding of FHBL but also enhances patient care in instances where metabolic and neuromuscular disorders coexist. These unique presentations underscore the importance of interdisciplinary collaboration in research and clinical practice, highlighting the need for comprehensive approaches to complex medical cases.

Case Presentation

A 21-year-old male presented to a primary care clinic with a chief complaint of muscle weakness, particularly in his upper extremities, which he has noticed over the past year. He reports difficulty performing pushups and other physical activities required by his military duties. There is no significant family history of neuromuscular disorders. He reports no allergies and is not on any regular medications. His physical training routine is rigorous, which brought his muscle weakness to attention.

The patient exhibited several issues in the right upper extremity, including decreased muscle bulk of the right infraspinatus muscle compared to the left, prominent scapular winging when pushing forward (more pronounced on the right side), and decreased facial excursion on smiling. No other significant abnormalities were noted.

These findings suggested subsequent differential diagnosis for facioscapulohumeral muscular dystrophy (FSHD1), proximal myopathy in the right upper extremity of other etiologies, and compressive neuropathy. Electromyography (EMG) confirmed that no nerve damage contributed to these symptoms without evidence of neuropathy. The patient also presented with a resolving compressive neuropathy of the right common peroneal nerve. This condition had essentially returned to normal motor function with residual sensory symptoms. While FSHD1 can involve peroneal motor functions, it typically does not cause sensory symptoms, suggesting this neuropathy may be unrelated to the upper extremity symptoms. Given the clinical suspicion of Facioscapulohumeral Muscular Dystrophy type 1 (FSHD1), specific testing was pursued. The FSHD1 Southern Blot was performed, which did not identify a contraction of the D4Z4 repeats on chromosome 4q35, indicating no conclusive evidence for Facioscapulohumeral Muscular Dystrophy type 1 (FSHD1) (Table 1).

Table 1: FSHD1 southern blot.

Variant identified	Result
Pathogenic contraction of D4Z4 repeats on Ch4q35 gene	No pathogenic contraction was identified. Do not completely rule out diagnosis as variants not detected by the assay

Southern blot analysis of the D4Z4 repeat region on chromosome 4q35 to assess facioscapulohumeral muscular dystrophy type 1 (FSHD1). No pathogenic contraction was detected, but diagnosis could not be entirely ruled out due to potential undetected variants.

Nevertheless, the diagnosis of FSHD1 could not be entirely ruled out due to potential variants not detected by this assay or variants in other genes. Together, the patient's clinical presentation, EMG findings, and the current negative FSHD1 Southern Blot suggest a proximal myopathy potentially related to an underlying genetic disorder, which warranted further genetic evaluation. The patient was further screened to evaluate additional potential contributing factors. Pertinent laboratory results included low levels of total cholesterol and LDL cholesterol, measuring 11 mg/dL and <30 mg/dL, respectively. HDL cholesterol was high at 71 mg/dL. Triglyceride levels were elevated at 115 mg/dL, while direct measurement of Low-Density Lipoprotein Cholesterol (LDL-C) was 39 mg/dl, and Lipoprotein a (Lpa) cholesterol levels showed decreased levels at 11.6 mg/dL.

Additional laboratory parameters included Creatine Kinase (CK) at 179 U/L, Vitamin D-25 OH level indicating deficiency, Vitamin A level elevated at 65.4 mcg/dL, Vitamin K level normal at 0.57 ng/mL, and Vitamin E Alpha Tocopherol level low at 5.6 mg/L (Table 2).

Table 2: Laboratory panel.

Lab Test	Result	Reference Range
Creatine kinase (CK)	179 U/L	Males: 55-170 U/L
Vitamin D-23 Hydroxy (OH)	10 ng/mL	20-80 ng/mL
Vitamin A	65.4 mcg/dL	20-60 mcg/dL
Vitamin K	0.57 ng/ml	0.10-2.2 ng/dL
Vitamin E alpha Tocopherol	5.6 mcg/mL	5.8-17 mcg/mL
Total Cholesterol	111 mg/dL	<200 mg/dL
High Density Lipoprotein (HDL)	71 mg/dL	>35 mg/dL
Low Density Lipoprotein Cholesterol (LDL-C)	<30 mg/dL	<100 mg/dL
Triglycerides	115 mg/dL	<150 mg/dL
LDL-Direct	39 mg/dL	<100 mg/dL
Lipoprotein a (Lpa)	11.6 mg/dl	< 30 mg/dL

Serum laboratory results demonstrating lipid abnormalities and vitamin deficiencies. Notable findings include markedly decreased total cholesterol and Low-Density Lipoprotein Cholesterol (LDL-C) levels, elevated High-Density Lipoprotein (HDL), and a deficiency in Vitamin D and Vitamin E.

A heterozygous single nucleotide substitution leading to a nonsense change denoted c.7564C>T at the cDNA level and p.(Arg2522*) at the protein level was identified in APOB (Table 3).

Table 3: Genetic analysis of APOB variant.

Variant identified	C.7564c>T, P.(Arg2522*) (Heterozygous)
Variant classification	Pathogenic
Gene name	Apob (Nm_000384.2)
Associated condition	Hypercholesterolemia, Familial, 2 (Autosomal Dominant), Hypobetalipoproteinemia (Autosomal Recessive)

Identification of a heterozygous pathogenic APOB variant (c.7564C>T, p.Arg2522*), associated with familial hypobetalipoproteinemia, an autosomal recessive disorder characterized by abnormally low levels of apolipoprotein B-containing lipoproteins.

This variant replaces the arginine with a premature stop codon and is expected to result in an absent or disrupted protein product. Loss-of-function variants in APOB are a known mechanism of disease [8]. This variant has been identified in a patient with familial hypobetalipoproteinemia [9] and documented in a registry for patients with disorders of lipoprotein metabolism [10]. Additional genetic testing using the Invitae Comprehensive Neuromuscular Disorders Panel was also pursued. This panel is designed to identify potential neuromuscular disorders by analyzing a wide range of genes associated with these conditions. The testing process involves analyzing the DNA sample for specific genetic variants that may be linked to neuromuscular disorders. In this particular case, the test identified several Variants of Uncertain Significance (VUS) in genes such as AMPD1, DMD, MAP3K20, TOP3A, and TTN (Table 4).

Table 4: Invitae comprehensive neuromuscular disorders panel.

Variant identified	Results
AMPD1 c.133C>T (p.Gln45*) heterozygous	Positive
DMD c.2681G>C (p.Ser894Thr) hemizygous	Positive
MAP3K20 c.1538C>T (p.Thr513Ile) heterozygous	Positive
TOP3A c.2264G>A (p.Gly755Asp) heterozygous	Positive
TTN c.106210G>A (p.Val35404Ile) heterozygous	Positive

Variants identified through the Invitae Comprehensive Neuromuscular Disorders Panel, including variants of uncertain significance in Adenosine Monophosphate Deaminase 1 (AMPD1), Duchenne Muscular Dystrophy (DMD), Mitogen-Activated Protein Kinase Kinase Kinase 20 (MAP3K20), DNA Topoisomerase III Alpha (TOP3A), and Titin (TTN) genes. These variants were analyzed for their potential association with neuromuscular disorders. The management mainly involved supportive care, including physical therapy to maintain muscle strength and function. Further interpretation of genetic results will provide further guidance for additional management decisions and ongoing monitoring.

Discussion

Our patient's unique clinical presentation, exhibiting both FHBL and neuromuscular symptoms, offers significant insights into the pleiotropic effects of genetic mutations. This case report explains the complexity of genetic disorders. It highlights the necessity for a comprehensive understanding of the multifaceted roles that multiple genetic mutations can play in various disease states. Mutations in the APOB, LDLR, and PCSK9 genes primarily cause FHBL. The APOB gene codes apolipoprotein B, a vital component of LDL particles, which is crucial for the transport and metabolism of cholesterol. Mutations in this gene impair the normal function of APOB, leading to defective LDL clearance and elevated cholesterol levels [11]. Among these, the C. 7564C>T mutation in APOB protein identified in our patient results in a truncated APOB protein.

This mutation has been documented in various genetic databases [12] but has not been extensively studied for its role in neuromuscular disorders. However, the same specific mutation, c.7564C>T, has been associated with neuromuscular symptoms in the analysis of the dystrophin gene in Duchenne muscular dystrophy [10]. This unique combination of symptoms suggests a potential interaction between lipid metabolism and neuromuscular function, an area that is not yet fully understood in medical literature.

The pathophysiology linking APOB mutations to muscular dystrophy-like symptoms is not well-characterized, presenting a significant challenge. Some literature suggests that lipid metabolism disorders can lead to secondary muscular complications due to lipid accumulation in muscle tissues, oxidative stress, and subsequent muscle damage [13]. Therefore, this case may represent the first reported instance of different genetic mutations manifesting with this unique combination of symptoms. Moreover, the patient was also tested for neuromuscular genetic disorders using the Invitae Neuromuscular Disorders Panel, and several genetic mutations were identified.

Titin (TTN), the gene encoding the giant protein titin, is critical for sarcomere structure and muscle contraction [14]. The c.106210G>A mutation (p.Val35404Ile) results in an amino acid substitution in the titin protein, potentially impairing its role in muscle elasticity and contraction. The relationship between TTN and FHBL, though less direct than the other two mutations, underscores the complex interplay between muscle and neuronal health. The patient tested positive for these. However, the mutations are classified as of uncertain significance due to limited evidence regarding their association with FHBL.

Topoisomerase 3 Alpha (TOP3A), encoding a DNA topoisomerase responsible for resolving DNA tangles during replication, is another gene of interest. The c.2264G>A (p.Gly755Asp) variant substitutes glycine with aspartic acid, which may affect DNA repair and genome integrity. Mutations in TOP3A have been associated with neurological disorders that share overlapping features with FHBL, including episodic ataxia and some types of epilepsy. Since topoisomerase dysfunction can lead to neuronal instability, it may contribute to the brainstem dysfunction seen in FHBL, exacerbating symptoms such as hemiplegia, dizziness, and sensory disturbances. Furthermore, given the importance of DNA repair in muscle cells, TOP3A mutations may also contribute to neuromuscular disorders, potentially leading to muscular dystrophy or other muscle weakness [15-17].

Adenosine Monophosphate Deaminase 1 (AMPD1) is an enzyme involved in purine metabolism, responsible for converting Adenosine Monophosphate (AMP) into Inosine Monophosphate (IMP), a crucial step for maintaining cellular energy balance, especially during high-intensity exercise. Although no direct relationship between AMPD1 mutations and FHLB has been firmly established, both disorders share common metabolic disruptions. AMPD1 deficiency has been shown to impair exercise performance by limiting anaerobic energy production, which could indirectly affect lipid metabolism, especially under stress conditions like exercise. This suggests that metabolic changes in AMPD1-deficient individuals might potentially influence lipid profiles, raising the possibility that AMPD1 mutations could have a secondary impact on lipid metabolism pathways similar to those affected in FHLB [18,19].

Furthermore, the biochemical interactions between purine and lipid metabolism may provide a framework for understanding any potential shared mechanisms between these two conditions. However, further research is needed to explore whether AMPD1 mutations contribute to developing lipid-related disorders like FHLB and establish possible genetic or biochemical links between purine metabolism and lipid metabolism disorders. Duchenne muscular dystrophy (DMD)is a genetic disorder caused by mutations in the dystrophin gene, which produces a crucial protein that stabilizes and strengthens muscle cells during activity. The absence of dystrophin leads to progressive muscle damage, weakness, and metabolic disturbances. Although primarily a neuromuscular condition, there is speculation about a possible link between DMD and FHBL, a genetic condition involving low cholesterol levels, typically due to mutations in APOB or PCSK9.

Mitogen-Activated Protein Kinase 20 (MAP3K200 encodes a protein involved in the MAP kinase signaling pathway, which is critical in neuronal growth, differentiation, and apoptosis. The c.1538C>T mutation, a missense variant (p.Pro513Leu), potentially disrupts the protein's kinase activity, which could affect neuronal excitability and ion channel function, mechanisms central to the pathophysiology of migraines.

Despite the inconclusive genetic findings, the combination of clinical evaluation, EMG results, and comprehensive genetic and laboratory testing provided substantial insight into the patient's condition. The negative consequence of the FSHD1 Southern Blot, coupled with the identified VUS, underscores the complexity of diagnosing neuromuscular disorders in young, active individuals and highlights the importance of comprehensive genetic testing and follow-up in achieving an accurate investigation, diagnosis, and follow-up.

In light of these findings, the different mutations in the APOB gene, combined with the patient's clinical symptoms, point to a novel phenotypic spectrum where multiple genetic mutations manifest in both FHBL and neuromuscular abnormalities. This finding challenges the traditional understanding of these conditions as separate entities and suggests they may share common genetic underpinnings.

Such cases underscore the importance of considering broader genetic testing and integrated diagnostic approaches in patients presenting complex or atypical clinical profiles. This case provides significant insight with the potential to broaden the understanding of the range of symptoms associated with APOB mutations. While familial hypobetalipoproteinemia is well-documented in the context of lipid metabolism disorders, the association with neuromuscular symptoms adds a new dimension to the clinical implications of APOB mutations. This case highlights the necessity of considering genetic disorders beyond their traditional presentations and the role of genetic testing in uncovering underlying pathologies that may not be apparent through routine diagnostic approaches.

Conclusions

From a clinical practice perspective, this case underscores the necessity of a multidisciplinary approach in diagnosing and managing patients with complex symptomatology that spans multiple systems. The patient's presentation, characterized by hypolipidemia and muscular dystrophy-like symptoms, necessitated a comprehensive diagnostic workup that included genetic testing, EMG, and extensive clinical evaluation. This thorough approach was crucial in identifying the underlying genetic mutation and providing a more precise diagnosis. Recognizing the pleiotropic effects of mutations can lead to more accurate diagnoses and personalized treatment plans, improving patient outcomes. Furthermore, adopting a holistic diagnostic approach that integrates clinical, biochemical, and genetic data can provide a more comprehensive understanding of the patient's condition and guide more effective management strategies.

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Manuscript Information: Received: March 31, 2025; Accepted: April 22, 2025; Published: April 30, 2025

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Citation: Ly L, Kaur J, Eid TJ, Mohamed I. Deciphering the genetic link between familial hypobetalipoproteinemia and neuromuscular disorder: A clinical case report. Open J Clin Med Case Rep. 2025; 2347.