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Case Study

# Caveolin 3 deficiency myopathy associated with dyslipidemia: Treatment challenges and possible pathophysiological association

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**KEYWORDS:**
Caveolin-3;
Hypercholesterolemia;
Rippling muscle disease;
Creatine kinase;
Electromyography test

**Abstract:** We report the case of a patient treated at the lipid clinic because of high cholesterol levels with consistently elevated creatine kinase concentrations that precluded statin treatment. Electromyography showed a rippling muscle disease pattern. A muscle biopsy confirmed caveolin 3 deficiency, and a missense mutation in the *CAV3 gene* was identified. The patient could be properly managed with ezetimibe and cholestyramine, which reduced the low-density lipoprotein cholesterol by 30%. He remains asymptomatic after 10 years of follow-up. Caveolae and caveolins are essential to membrane integrity, and their deficit has been associated with insulin resistance and hypercholesterolemia in animal models. Therefore, a putative pathophysiological association between myopathy and lipid metabolism mediated by functional alterations of membrane receptors is considered.


## Introduction

Caveolins (CAVs) are structural components of cell membranes. CAVs form membrane caveolae, which are 60 to 80 nm wide pits that are heterogeneously distributed in plasma membranes.[1–3] CAVs are crucial drivers of caveolae formation; in particular, CAV1 and CAV3 are essential for the formation of caveolae.[4] Caveolae have several roles, including shape, integrity, and molecular order at the membrane level. There are 3 CAV forms in mammals, which are differentially expressed in tissues: CAV1 and CAV2 are expressed in hepatocytes, adipocytes, and other non-skeletal muscle cells, whereas CAV3 is predominantly expressed in striated muscle but also expressed in cardiomyocytes and smooth muscle cells.[5] CAVs participate in endocytosis processes and modulation of intracellular signalling.[6] Interestingly, caveolae are involved in not only cellular metabolic regulation through calcium signaling but also glucose and lipid metabolism.[5] A lack of CAV in adipocytes has been associated with increased insulin receptor degradation.[7] Caveolae provide

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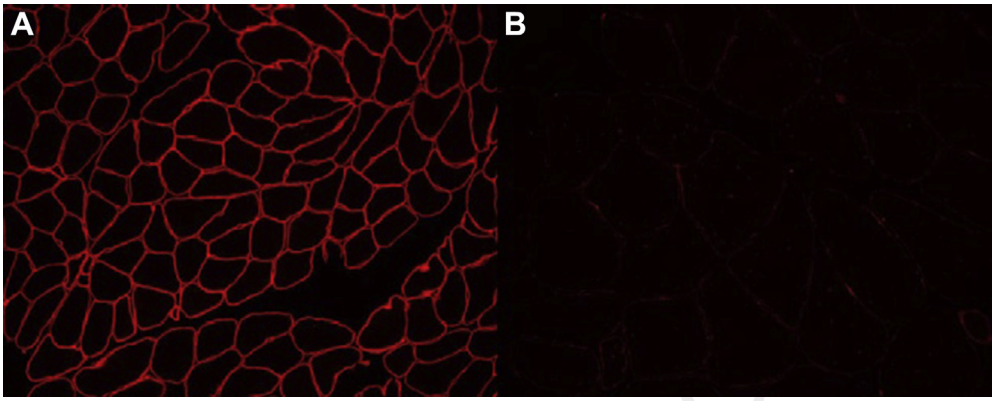


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**Figure 1** Rhodamine-labeled immunofluorescence where caveolin 3 is observed on the membrane in the control case (A) but is barely present in the patient case (B).

an important contribution to the cell surface area of adipocytes and may facilitate lipid fatty acid trafficking.[8] Furthermore, CAVs have been associated with high-density lipoprotein transcytosis, and their deficit leads to hyperlipidemia[9] by mechanisms that are currently not well understood. CAV3 participates in all the previously mentioned CAV functions. Its deficit is associated with 4 myopathy phenotypes, including limb girdle muscular dystrophy 1C, isolated high creatine kinase (CK), distal myopathy, and rippling muscle disease (RMD), with clinical manifestations ranging from asymptomatic to severe muscle weakness.[10–12] RMD is a rare myopathy that is generally benign and sometimes asymptomatic and that can present as myotonic-like myopathy associated with rapid rolling and percussion-induced contractions.[13,14] Thirty different mutations of the *CAV3* gene have been reported in humans. The same mutation can be expressed with different clinical phenotypes and symptoms that may overlap.[15]

The *CAV3* deficit has been associated with insulin resistance and hypercholesterolemia in animal models. *CAV3* knockout mice show increased adiposity and whole body insulin resistance, probably mediated by ligand-induced insulin receptor instability in skeletal muscles.[16]

There is only 1 publication documenting *CAV3* p-A46 T missense mutation related to RMD.[17] Thirty-nine members of the same family were studied, but not all members presented with hyperCKemia or rippling. This disease seems to be homogeneous, benign, and not progressive.

In this report, we describe the clinical case of an asymptomatic patient affected by CAV3 deficiency who was treated at our lipid clinic because of high cholesterol levels mimicking familial hypercholesterolemia (FH) with high CK levels precluding the use of statins. We discuss his clinical management difficulties because of the CK levels and the possible pathogenic relationship between CAV3 deficiency and lipoprotein alteration.

## Clinical case

A 45-year-old male patient was sent to our metabolic unit because of high low-density lipoprotein (LDL) cholesterol (LDL-C) and high CK levels that hampered his clinical management. His 3 children have neither high CK levels nor hyperlipidemia. Four brothers and 5 sisters, who live abroad, have no evidence of CK alterations. Three brothers have non-confirmed hyperlipidemia. He had no major cardiovascular risk factors. No antecedents of relevant diseases were reported. The patient was

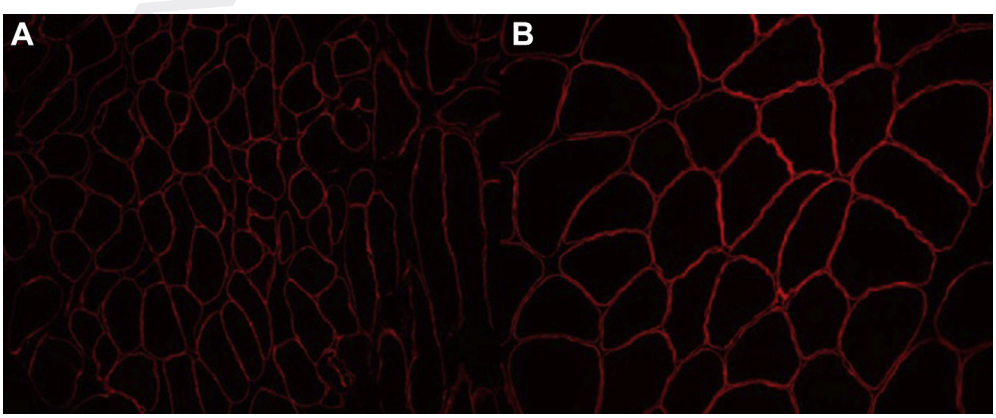


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**Figure 2** The image showing labeling for dystrophin does not show differences between the control (A) and the patient (B).