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CONTEXT: Berardinelli-Seip congenital lipodystrophy (BSCL) is a rare recessive disease characterized by near absence of adipose tissue, resulting in severe dyslipidemia and insulin resistance. In most reported cases, BSCL is due to alterations in either seipin, of unknown function, or 1-acylglycerol-3-phosphate acyltransferase-beta (AGPAT2), which catalyzes the formation of phosphatidic acid.

OBJECTIVE: We sought to determine the genetic origin of the unexplained cases of BSCL. We thus sequenced CAV1, encoding caveolin-1, as a candidate gene involved in insulin signaling and lipid homeostasis. CAV1 is a key structural component of plasma membrane caveolae, and Cav1-deficient mice display progressive loss of adipose tissue and insulin resistance.

DESIGN: We undertook phenotyping studies and molecular screening of CAV1 in four patients with BSCL with no mutation in the genes encoding either seipin or AGPAT2.

RESULTS: A homozygous nonsense mutation (p.Glu38X) was identified in CAV1 in a patient with BSCL born from a consanguineous union. This mutation affects both the alpha- and beta-CAV1 isoforms and ablates CAV1 expression in skin fibroblasts. Detailed magnetic resonance imaging of the proband confirmed near total absence of both sc and visceral adipose tissue, with only vestigial amounts in the dorsal sc regions. In keeping with the lack of adipose tissue, the proband was also severely insulin resistant and dyslipidemic. In addition, the proband had mild hypocalcemia likely due to vitamin D resistance.

CONCLUSIONS: These findings identify CAV1 as a new BSCL-related gene and support a critical role for caveolins in human adipocyte function.

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