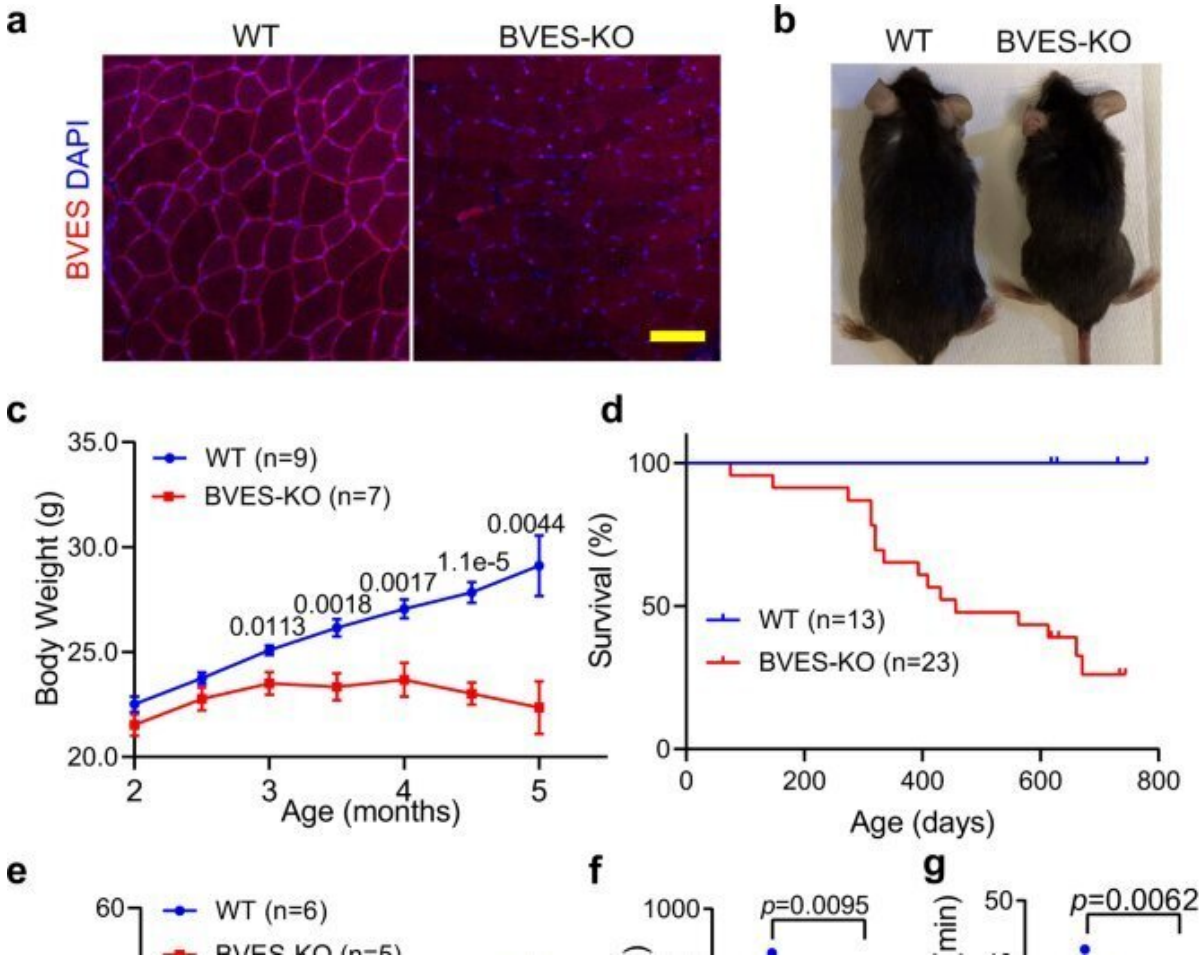
Researchers investigate the protein BVES and its important role in muscular dystrophy

April 5 2023, by Jackie Maupin



BVES disruption compromises the body weight gain and muscle function in mice. All animal experiments were performed in WT and BVES-KO male mice with the C57BL/6N genetic background. a Immunofluorescence images of GA muscles in WT and BVES-KO mice (4 months of age) stained with the antibody against BVES and DAPI. Scale bar: 100 μm. (n = 4 per genotype). b

Representative image of WT and BVES-KO male littermates at 4 months of age. c, Body weight gain of male BVES-KO and age/sex-matched WT mice from two to five months of age. Two-tailed paired Student's t test. d Kaplan–Meier survival curve of WT and BVES-KO male mice. e Voluntary wheel running of BVES-KO and age-matched WT male mice (4 months of age). f, g Endurance capacity test performed by treadmill running showing running distance (f) and time to exhaustion (g) in BVES-KO (n = 5) and WT (n = 5) male mice (4 months of age). Two-tailed unpaired Student's t test. h The number of dropouts to test the capacity of recovery from muscle injury on the treadmill in BVES-KO and WT male mice (6 months of age). Two-tailed paired Student's t test. i Tetanic torque measurements of the posterior compartment muscles of BVES-KO and WT male mice in age-dependent manner (2-month age: WT (n = 11), BVES-KO (n = 9); 4-month age: WT (n = 9), BVES-KO (n = 9); 6-month age: WT (n = 9), BVES-KO (n = 8)). ns indicates no significant difference. Two-way ANONA with Tukey's multiple comparisons test. Data are mean ± SEM. Source data are provided as a Source Data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-37496-8

A study by Indiana University School of Medicine researchers sheds new light on the development and treatment of a rare form of muscular dystrophy. The study's findings were recently published in *Nature Communications*.

Muscular dystrophies are a group of muscle diseases caused by gene mutations. There are several major varieties, including limb-girdle muscular dystrophy. According to the Centers for Disease Control, about 2 in 100,000 people are affected by various subtypes of limb-girdle muscular dystrophy which can develop at any age.

"Being a relatively new form of muscular dystrophy, very little is known about the development of limb-girdle muscular dystrophy type 25 and there is no treatment available for patients," said Renzhi Han, Ph.D., professor of pediatrics at the Herman B Wells Center for Pediatric

Research and the senior author of the article. "Our study's main goal was to understand the molecular pathogenesis of muscular dystrophy caused by genetic mutations in BVES and develop a therapeutic treatment for this form of the disease."

The study investigated the role of blood vessel epicardial substance (BVES) protein in the development of muscular dystrophy and atrophy. The researchers found that the study's model engineered to lack BVES showed symptoms similar to those observed in humans. Further investigation showed that BVES interacts with an enzyme called ADCY9, inhibiting its activity in synthesizing cyclic AMP, an important signaling molecule in many biological processes.

The study also found the absence of BVES resulted in overactive ubiquitin proteasome degradation. Importantly, bortezomib, a specific inhibitor of ubiquitin proteasome degradation approved by the United States Food and Drug Administration for the treatment of certain cancers, significantly ameliorates the pathology of BVES-knockout skeletal muscle. Overall, these findings suggest that BVES may play a crucial role in maintaining muscle health and pharmacological treatments inhibiting proteasome degradation may be effective in alleviating BVES-deficient muscular dystrophy.

"Understanding the underlying causes of muscular dystrophy gets us one step closer to finding cures for patients," said Haiwen Li, Ph.D., postdoctoral fellow and co-author of the published study. "Our research sheds new light on therapeutic treatment options for patients with BVES mutations and it will lead to additional important investigations to help other diseases."

In addition to muscular dystrophy, BVES mutations are also linked to cardiac arrhythmia and cancer. Looking ahead, the researchers plan to investigate the roles of gene mutations in other health issues. They

previously performed a preclinical study that demonstrated adeno-associated virus-BVES can improve muscle pathology and function in a mouse model with limb-girdle muscular dystrophy type 25. Results from that research were published in *Molecular Therapy*.

More information: Haiwen Li et al, Defective BVES-mediated feedback control of cAMP in muscular dystrophy, *Nature Communications* (2023). DOI: 10.1038/s41467-023-37496-8

Provided by Indiana University School of Medicine