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Collaboration between psychologists and economists

Properties of glasses

New Middle Pleistocene hominin cranium

Chromosome Y and susceptibility to influenza

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PNAS (ISSN-0027-8424) is published weekly by the National Academy of Sciences.

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Cover image: Pictured is a modern plains bison cow from Elk Island National Park, Alberta, Canada. Duane Froese et al. report on the oldest well-dated bison fossils in North America, including a steppe bison (*Bison priscus*) from northern Yukon and a giant long-horned bison (*Bison latifrons*) from Colorado. Based on ancient bison mitochondrial genomes, the study finds that all modern bison are descended from a dispersal of bison between 195,000 and 135,000 years ago from Eurasia via the Bering Land Bridge and a subsequent dispersal approximately 45,000 and 21,000 years ago. See the article by Froese et al. on pages 3457–3462. Image courtesy of John W. Ives (University of Alberta, Edmonton, Canada).

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Loss of LMOD1 impairs smooth muscle cytocontractility and causes megacystis microcolon intestinal hypoperistalsis syndrome in humans and mice

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Edited by Eric N. Olson, University of Texas Southwestern Medical Center, Dallas, TX, and approved February 21, 2017 (received for review December 13, 2016)

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a congenital visceral myopathy characterized by severe dilation of the urinary bladder and defective intestinal motility. The genetic basis of MMIHS has been ascribed to spontaneous and autosomal dominant mutations in actin gamma 2 (ACTG2), a smooth muscle contractile gene. However, evidence suggesting a recessive origin of the disease also exists. Using combined homozygosity mapping and whole exome sequencing, a genetically isolated family was found to carry a premature termination codon in *Leiomodin1 (LMOD1)*, a gene preferentially expressed in vascular and visceral smooth muscle cells. Parents heterozygous for the mutation exhibited no abnormalities, but a child homozygous for the premature termination codon displayed symptoms consistent with MMIHS. We used CRISPR-Cas9 (CRISPR-associated protein) genome editing of *Lmod1* to generate a similar premature termination codon. Mice homozygous for the mutation showed loss of LMOD1 protein and pathology consistent with MMIHS, including late gestation expansion of the bladder, hydronephrosis, and rapid demise after parturition. Loss of LMOD1 resulted in a reduction of filamentous actin, elongated cytoskeletal dense bodies, and impaired intestinal smooth muscle contractility. These results define *LMOD1* as a disease gene for MMIHS and suggest its role in establishing normal smooth muscle cytoskeletal–contractile coupling.

CRISPR-Cas9 | genetics | Leiomodin | myopathy | smooth muscle

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) (MIM155310) is a rare congenital defect of visceral smooth muscle, primarily affecting females who present at birth with functional obstruction of intestine, microcolon, dilation of bladder, and secondary hydronephrosis. More than 250 cases have been reported since the initial description of MMIHS in five young girls in 1976 (1–3). Total parenteral nutrition (TPN), adequate intermittent catheterization of bladder, and surgical corrections for intestinal malrotation are frequent modes of treatment for this disease without which rapid death ensues. In some instances, multivisceral organ transplantation has been indicated with some success. Despite these clinical interventions, MMIHS often leads to premature death due to complications of therapy (3, 4).

The majority of MMIHS cases are sporadic, stemming from de novo, heterozygous missense mutations in the smooth muscle-restricted *ACTG2* gene (5, 6). These mutations are thought to render the *ACTG2* protein defective for normal actin polymerization and contractile activity in visceral smooth muscle organs although formal in vivo proof for this *ACTG2* loss of function is

lacking (6, 7). Heterozygous mutations in *ACTG2* are also observed in patients with autosomal dominant MMIHS (6, 8), but there is emerging evidence for a recessive mode of inheritance. For example, a homozygous loss-of-function variant in the myosin heavy chain 11 (*MYH11*) gene, which is another highly specific contractile gene for smooth muscle lineages (9), was reported in a patient with MMIHS from a consanguineous (i.e., genetically related) couple (10). To date, no other smooth muscle-restricted contractile genes have been linked to MMIHS.

In this report, a patient with MMIHS is described from a consanguineous couple in whom no variants of *ACTG2* or *MYH11* were found. Rather, an autosomal recessive inherited subtype of MMIHS has been discovered involving a homozygous nonsense mutation in *Leiomodin1 (LMOD1)*, an understudied smooth muscle-restricted gene (11) that is a direct target of the

Significance

Rare recessive monogenic diseases are often found in isolated populations. In one such population, we identified a child carrying a homozygous nonsense mutation in an understudied smooth muscle-restricted gene called *Leiomodin1 (LMOD1)*. Heterozygous parents showed no disease; however, the child died shortly after birth from a rare condition known as megacystis microcolon intestinal hypoperistalsis syndrome. A mouse model with a similar *Lmod1* mutation, engineered with CRISPR-Cas9 genome editing, exhibited the same gastrointestinal and urinary bladder phenotypes as seen in the newborn child. Phenotyping revealed insights into the underlying cause of the disease. Results demonstrate the conserved function of LMOD1 in human and mice and the importance of this protein in the molecular regulation of contractility in visceral smooth muscle cells.

Author contributions: D.H., M.P.W., D.O., Y.H., V.N., T.D., W.Y., M.M.A., R.M.W.H., and J.M.M. designed research; D.H., M.P.W., D.O., E.B., J.B.G.M.V., Y.H., Q.L., H.S., R.W.W.B., W.F.J.v.I., O.J.S., C.C., K.L.d.M.B., S.X., W.Y., M.M.A., and J.M.M. performed research; D.H., M.P.W., E.B., J.B.G.M.V., M.D., A.J.B., K.L.d.M.B., A.S.B., D.T., Z.G.J., T.D., M.M.A., R.M.W.H., and J.M.M. analyzed data; and D.H., M.P.W., R.M.W.H., and J.M.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1620507114/-DCSupplemental.