Hereditary myopathy with early respiratory failure

Hereditary myopathy with early respiratory failure (HMERF) is an inherited disease that affects muscles used for movement (skeletal muscles) and muscles that are needed for breathing (respiratory muscles).

The major signs and symptoms of HMERF usually appear in adulthood, often in the mid-thirties. Among the earliest signs of the condition are breathing problems and difficulty walking. Weakness of the respiratory muscles, particularly the diaphragm (the muscle that separates the organs in the abdomen from those in the chest), causes breathing problems. This weakness worsens over time and can lead to life-threatening respiratory failure. Some affected individuals have weakness of muscles of the lower leg and foot, which makes it difficult to lift the toes while walking, a condition known as foot drop. Other muscles that become weak in people with HMERF include those of the hips, thighs, upper arms, and neck.

When viewed under a microscope, muscle fibers from affected individuals contain abnormal structures called cytoplasmic bodies. In many cases, the cytoplasmic bodies are arranged side-by-side in a ring inside the muscle fiber, resembling a necklace (necklace cytoplasmic bodies).

Frequency

HMERF is a rare condition with an unknown prevalence. It has been found in populations worldwide.

Causes

HMERF is caused by mutations in the *TTN* gene. This gene provides instructions for making a protein called titin. Titin plays an important role in muscles the body uses for movement (skeletal muscles) and in heart (cardiac) muscle.

Within muscle cells, titin is an essential component of structures called sarcomeres. Sarcomeres are the basic units of muscle contraction; they are made of proteins that generate the mechanical force needed for muscles to contract. Titin has several functions within sarcomeres. One of its most important jobs is to act as a backbone in these structures, providing structure, flexibility, and stability. Titin also plays a role in chemical signaling and in assembling new sarcomeres.

The *TTN* gene mutations responsible for HMERF lead to the production of an altered version of the titin protein that cannot fold into its normal 3-dimensional shape. Researchers are studying how abnormally folded titin contributes to the muscle damage that underlies the signs and symptoms of HMERF. It is unclear why these effects are

usually limited to skeletal muscles and respiratory muscles, and do not involve cardiac muscle.

Rarely, people with the characteristic features of HMERF do not have identified mutations in the *TTN* gene. In these cases, the genetic cause of the condition is unknown.

Inheritance Pattern

HMERF is typically inherited in an autosomal dominant pattern, which means one copy of the altered *TTN* gene in each cell is sufficient to cause the disorder. An affected person usually has one parent with the condition.

In rare cases, a specific mutation in one copy of the *TTN* gene leads to mild signs and symptoms of the condition, such as respiratory problems that begin later than is typical in HMERF with no other muscle weakness. However, family members who have the mutation in both copies of the gene have severe features of HMERF.

Other Names for This Condition

- Edstrom myopathy
- HMERF
- myopathy, proximal, with early respiratory muscle involvement

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Hereditary myopathy with early respiratory failure
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1863599/

Other Diagnosis and Management Resources

- GeneReview: Hereditary Myopathy with Early Respiratory Failure (HMERF)
  https://www.ncbi.nlm.nih.gov/books/NBK185330
- National Heart, Lung, and Blood Institute: Respiratory Failure Diagnosis
  https://www.nhlbi.nih.gov/health-topics/respiratory-failure#Diagnosis
- National Heart, Lung, and Blood Institute: Respiratory Failure Treatment
  https://www.nhlbi.nih.gov/health-topics/respiratory-failure#Treatment

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Muscle Disorders
  https://medlineplus.gov/muscledisorders.html
- Health Topic: Respiratory Failure
  https://medlineplus.gov/respiratoryfailure.html

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Congenital Myopathy
  https://www.ninds.nih.gov/Disorders/All-Disorders/Congenital-Myopathy-Information-Page

Educational Resources

- MalaCards: hereditary myopathy with early respiratory failure
  https://www.malacards.org/card/hereditary_myopathy_with_early_respiratory_failure
- Merck Manual Consumer Version: Respiratory Failure
  https://www.merckmanuals.com/home/lung-and-airway-disorders/respiratory-failure-and-acute-respiratory-distress-syndrome/respiratory-failure
- Orphanet: Hereditary myopathy with early respiratory failure
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=178464

Patient Support and Advocacy Resources

- Congenital Muscle Disease International Registry
  https://www.cmdir.org/
- Muscular Dystrophy Association
  https://www.mda.org/
- Muscular Dystrophy Canada
  http://www.muscle.ca/
- Muscular Dystrophy UK
  https://www.musculardystrophyuk.org/
- Resource List from the University of Kansas Medical Center: Muscular Dystrophy / Atrophy
  http://www.kumc.edu/gec/support/muscular.html

Clinical Information from GeneReviews

- Hereditary Myopathy with Early Respiratory Failure (HMERF)
  https://www.ncbi.nlm.nih.gov/books/NBK185330

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28hmerf%5BTIAB%5D%29+OR+%28%28dominant+myopathy%5BTIAB%5D%29+AND+%28early+respiratory+muscle%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

Catalog of Genes and Diseases from OMIM

- MYOPATHY, MYOFIBRILLAR, 9, WITH EARLY RESPIRATORY FAILURE
  http://omim.org/entry/603689

Medical Genetics Database from MedGen

- Hereditary myopathy with early respiratory failure
  https://www.ncbi.nlm.nih.gov/medgen/350930

Sources for This Summary

- Hedberg C, Toledo AG, Gustafsson CM, Larson G, Oldfors A, Macao B. Hereditary myopathy with early respiratory failure is associated with misfolding of the titin fibronectin III 119 subdomain. Neuromuscul Disord. 2014 May;24(5):373-9. doi: 10.1016/j.nmd.2014.02.003. Epub 2014 Feb 15.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24636144
- Palmio J, Evilä A, Chapon F, Tasca G, Xiang F, Brådvik B, Eymard B, Echaniz-Laguna A, Laporte J, Kärppä M, Mahjneh I, Quinlivan R, Laforêt P, Damian M, Berardo A, Taratuto AL, Bueri JA, Tommiska J, Raivio T, Tuerk M, Gölitz P, Chevessier F, Sewry C, Norwood F, Hedberg C, Schröder R, Edström L, Oldfors A, Hackman P, Udd B. Hereditary myopathy with early respiratory failure: occurrence in various populations. J Neurol Neurosurg Psychiatry. 2014 Mar;85(3):345-53. doi: 10.1136/jnnp-2013-304965. Epub 2013 Apr 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23606733
- Tasca G, Mirabella M, Broccolini A, Monforte M, Sabatelli M, Biscione GL, Piluso G, Gualandi F, Tonali PA, Udd B, Ricci E. An Italian case of hereditary myopathy with early respiratory failure (HMERF) not associated with the titin kinase domain R279W mutation. Neuromuscul Disord. 2010 Nov;20(11):730-4. doi: 10.1016/j.nmd.2010.07.269. Epub 2010 Aug 13.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20708934
- Tasca G, Udd B. Hereditary myopathy with early respiratory failure (HMERF): Still rare, but common enough. Neuromuscul Disord. 2018 Mar;28(3):268-276. doi: 10.1016/j.nmd.2017.12.002. Epub 2017 Dec 12. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29361395

- Toro C, Olivé M, Dalakas MC, Sivakumar K, Bilbao JM, Tyndel F, Vidal N, Farrero E, Sambuughin N, Goldfarb LG. Exome sequencing identifies titin mutations causing hereditary myopathy with early respiratory failure (HMERF) in families of diverse ethnic origins. BMC Neurol. 2013 Mar 20;13:29. doi: 10.1186/1471-2377-13-29.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23514108
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3610280/
- Uruha A, Hayashi YK, Oya Y, Mori-Yoshimura M, Kanai M, Murata M, Kawamura M, Ogata K, Matsumura T, Suzuki S, Takahashi Y, Kondo T, Kawarabayashi T, Ishii Y, Kokubun N, Yokoi S, Yasuda R, Kira J, Mitsuhashi S, Noguchi S, Nonaka I, Nishino I. Necklace cytoplasmic bodies in hereditary myopathy with early respiratory failure. J Neurol Neurosurg Psychiatry. 2015 May;86(5): 483-9. doi: 10.1136/jnnp-2014-309009. Epub 2014 Sep 24.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25253871

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