HRG HIBM Research Group
Non-profit molecular laboratory

IBM2 / HIBM / DMRV [*GNE*]

Information for Clinicians

Summary: Hereditary Inclusion Body Myopathy type 2 (IBM2) is an autosomal recessive adult onset muscle wasting disease worldwide. It is progressive and often leads to severe physical disability. Although IBM2 is a very rare disease worldwide, it is a common cause of disability in people of Iranian-Jewish heritage due to the founder Middle-Eastern mutation (*GNE:*p.M712T). The carrier (heterozygous) rate in Iranian-Jewish descendants is 1/15 – 1/20, and prevalence rate of disease (homozygous) is around 1/500 – 1/1500.

Indications for GNE:p.M712T Genotyping Test	**Specimen Requirements:** Buccal swab, or 4 ml of whole blood in an EDTA Vacutainer (lavender top), and completed requisition form. **Turnaround time:** 2-5 business days. Urgent testing with one business day turn-around can be provided at 25% additional cost.
• High risk population (Iranian or Middle-Eastern Jewish) • Family history of HIBM • Symptomatic, adult onset quadriceps sparing myopathy (consider sequencing entire coding region of GNE if patient is not of Iranian-Jewish decent).	

Interfering substances: Bone marrow recipients, or recipients of blood transfusion within the past 6 months, may show the genotype of the donor. In such patients, buccal swab specimen is preferred for testing. Additionally, substances that may inhibit nucleic acid amplification (e.g. some lipsticks) may prohibit us from performing the test.

Hereditary Inclusion Body Myopathies (HIBM) are a group of muscle wasting disorders, which are uncommon in the general world population. An autosomal recessive form of HIBM is known as IBM2, which is a common genetic disorder amongst people of Iranian-Jewish descent. IBM2 has also been identified in other minorities throughout the world. Patients of Asian (Japanese and others), European, and South American origin, as well as Muslim patients in the Middle Eastern, Palestinian, and Iranian origin, have been identified. In Japan and many East Asian countries, this disorder is known as Distal Myopathy with Rimmed Vacuoles (**DMRV**). It is also known as **Nonaka** type myopathy, Quadriceps Sparing Myopathy (**QSM**), or GNE related myopathy. This disorder is formally classified on Mendelian Inheritance in Man (MIM) as OMIM:600737 (IBM2) or OMIM:605820 (DMRV).

IBM2 causes progressive muscle weakness and wasting that usually starts around the age of 20 - 30 years and can progress to marked disability within 10 - 15 years, confining many patients to the wheelchair. The quadriceps are relatively spared, and remain strong until the late stages of disease, which is the reason IBM2 is often referred to as Quadriceps Sparing Myopathy (QSM). Early signs include difficulty walking on heels, difficulty running, weak index finger, and frequent loss of balance. On muscle biopsy, typical finding include inclusion bodies, rimmed vacuoles and accumulation of aberrant proteins similar to those found in senile plaques of Alzheimer's Brain disease (amyloid beta, hyperphosphorylated tau, amongst others). The most useful information for accurate diagnosis is the symptoms and weakness pattern. **If the quadriceps are spared but the hamstrings and iliopsoas are severely affected in a person between ages of 20 – 40, HIBM should be considered near the top of the differential diagnosis.**

Most believe typical clinical weakness pattern in persons of age 20-50 years, and positive genetic testing is sufficient for diagnosis. The following additional tests may be useful to confirm diagnosis of IBM2 and rule our other common causes of muscle weakness: Blood test for serum Creatine Kinase (CK or CPK); Nerve Conduction Study (NCS) / Electomyography (EMG); Muscle Biopsy; Magnetic Resonance Imaging (MRI) or Computer Tomography (CT) Scan to determine true sparing of quadriceps; Blood or Buccal Swab for genetic testing.