Short Report

Prevalence of GNE p.M712T and hereditary inclusion body myopathy (HIBM) in Sangesar population of Northern Iran


GNE myopathy or hereditary inclusion body myopathy (HIBM) is an ultra-rare severely disabling autosomal recessive adult onset muscle disease which affects roughly one to three individuals per million worldwide. Genetically, HIBM is caused by mutations in the glucosamine (UDP-\(\text{N}-\text{acetyl}\))2-epimerase/\(\text{N}-\text{acetylmannosamine}\) kinase gene (GNE), resulting in diminished enzyme function and reduced sialic acid biosynthesis. A founder variant GNE p.M712T was first described in patients of Iranian and Middle-Eastern descent living outside of Iran. Asymptomatic heterozygote or carrier frequency has been reported as high as 1 in 11 within the Persian-Jewish community residing in Los Angeles, CA. To investigate the prevalence of the p.M712T variant in Iran, we studied 792 samples collected from random individuals in Sangesar (Mahdishahr) in Northern Iran. DNA samples were obtained by buccal swab, and genotyping was performed by melting curve analysis. The results included 31 of 792 (3.91%) heterozygous carriers and 5 (0.31%) homozygotes for GNE p.M712T. All five homozygous individuals, age 30–64 years, were already symptomatic at the start of the study. Our findings suggest that the prevalence of GNE p.M712T is higher in the Sangesar population, comprised mostly of Muslim and Bahai descendants, compared with the general world population. Additional HIBM distribution studies are warranted within various subpopulations of Iran.

Conflict of interest

None of the authors have competing or financial conflict of interest.

The autosomal recessive form of hereditary inclusion body myopathy (HIBM) is a progressive neuromuscular disorder with early adult onset originally described in clusters of Japanese patients as Nonaka myopathy (1), and in patients of Iranian-Jewish descent as vacuolar myopathy sparing the quadriceps (2). HIBM initially affects the distal muscles and progresses to involve proximal muscles with the usual characteristic of quadriceps sparing (3). As distal muscle weakness is the presenting symptom in most patients and rimmed vacuoles are seen in microscopic examination of muscle biopsy, HIBM is also known as distal myopathy with rimmed vacuoles – dystrophy – epidemiology – IBM2 – muscle – Nonaka myopathy – orphan disease – Persia – Persian – quadriceps sparing myopathy – rare disease – sialic acid.

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rimmed vacuoles containing amyloid, and numerous aberrant non-specific proteins, including hyperphosphorylated tau and presenilin (2, 7, 8). The most common HIBM-related mutation is the Middle-Eastern founder allele p.M712T (atg>acg) in exon 12 of GNE (3). A more recent report suggests the carrier frequency is as high as 1 in 11 individuals of Persian-Jewish descent residing in Southern California (9). Another founder mutation, the p.V572L (gtg>cgt) in exon 10, has been observed in a cluster of Asian families (10, 11). Numerous additional allelic variations in GNE have been reported in other population (12–16). The onset of muscle weakness in HIBM typically occurs between the ages of 20 and 40 years, with serum creatine phosphokinase levels remaining normal or slightly elevated (2). The muscle weakness progresses over the next 10–20 years, with relative sparing of the quadriceps until the most advanced stages of the disease. The histopathology of an HIBM muscle biopsy reveals rimmed vacuoles on Gomori’s trichrome stain, small fibers in groups and tubulofilaments without evidence of inflammation. Although HIBM is considered an autosomal recessive disease and its carriers usually show no or only slight muscular weakness, a recent study in a family affected by HIBM revealed that the exon deletion of GNE in a single allele of the gene can lead to mild distal weakness later in life (17).

In this report we present our findings on the prevalence of the p.M712T mutation in a random sample of the Sangesar population. Sangesar (also known as Mahdishahr; 35° 42′ 39″ N and 53° 21′ 14″ E) is a city located on the southern slopes of the Alborz Mountains and is part of Semnan province near the Mazandaran province boundary (Fig. 1). According to census estimates in 2006, Sangesar had a population of 20,581 in 5473 families. This population is mostly of Muslim and Bahai background. The local leaders of the Bahai community estimate that many Bahai people of Sangesar migrated out of Iran following the revolution of 1979, and the majority of Sangesari-Bahai moved to the United States. The first Sangesari HIBM patient was diagnosed in 2010. Subsequently, several other myopathic individuals have been genotyped and confirmed as HIBM patients with the homozygous p.M712T mutation. In order to determine the frequency of this mutation in Sangesar, we conducted a limited population screen for prevalence of GNE p.M712T in this relatively isolated community of Northern Iran.

Materials and methods

Study population

Data collection and processing of this investigation were approved by the institutional review board of Semnan University of Medical Sciences in Semnan, Iran. Because many of the Sangesar residents were non-literate, verbal informed consent was obtained for each participant who was read a script of the formal consent form. A total of 792 random individuals participated in the study.

Genotyping evaluation

DNA was obtained using standard cotton tip swabs, and an assay for GNE p.M712T was performed for each patient as previously described (18).

Statistical analysis

The prevalence and their standard errors and 95% confidence bounds were estimated using the generalized estimating equation method, which takes into account the non-independence of multiple individuals in the same family (clustering within family).

Results

High quality DNA was obtained from 792 samples from random individuals in 300 families. We found 31 heterozygous (3.91%) carriers among 22 families (Fig. 2). In addition to the heterozygotes, there were five homozygous samples bearing the p.M712T mutation (0.63%), two of which belonged to the same family (sample numbers 69 and 81; see Table 1). Our results showed a relatively high prevalence of homozygous (1/25) individuals among the Sangesar population compared with the Japanese population in which the frequency of the disease reportedly approaches 1.7–3.5 per million (19).

Discussion

The use of multiple HIBM animal models has led to the novel insights into both the disease and the role of GNE/MNK in the pathophysiology of this disease. Recent advances in therapeutic approaches to treating HIBM include administration of ManNAc, a precursor
of Neu5Ac (15, 20), gene therapy (21, 22), and sialic acid (23, 24). Clarification of the prevalence of HIBM worldwide would be helpful for trial design and clinical drug development.

Although the p.M712T mutation is the most common mutation among the Middle Eastern Jewish population, it has also been observed in several non-Jewish populations (15). Because marriage between members of the Sangesar community and the people of Shahmirzad (a city with Jewish families located 6 km from Sangesar) is fairly common, it is conceivable that a subset of the present day Sangesar population is of relatively recent Jewish descent. Further analyses of M712T-associated HIBM patients and carriers living in this region may shed light on whether the Sangesar M712T mutation is related to the Iranian-Jewish haplotype and/or is related to the Jewish diaspora in the Middle East. Further studies within Iran may shed light on whether the M712T variant emerged originally within Jewish or non-Jewish ancient Iranian populations.

Interestingly, most of the identified patients with HIBM or HIBM-like symptoms hospitalized in the ‘Welfare and Rehabilitation Centre’ in Semnan (which serves all patients of Semnan province) belong to the Sangesar population.

Surprisingly, among the 792 individuals evaluated, 7 of those whose genotyping analysis did not show the M712T mutation (genotyped as wild-type) had clinical muscle weakness. If further clinical analyses confirm HIBM-like symptoms in this subset of patients, then gene sequencing of the entire GNE would be helpful for assessing mutations other than M712T. The presence of different mutations in GNE (p.V367I) has previously been reported in Iranian patients (25).

A non-homogenous age of onset has been already observed and described in HIBM patients (26). One possible hypothesis that might explain differences in the age of onset among HIBM patients is dietary influence. The people of this region traditionally produce and eat food products made from whey (the most frequently consumed are ‘Arshe’ and ‘Lour’). Several studies have shown that whey contains sialic acid (N-acetylenuramic acid) (27–29). This is noteworthy because sialic acid has been proposed as a potentially efficacious drug for HIBM patients, at least according to pre-clinical evidence in HIBM-affected mice and in a human cell line in vitro. The consumption of products rich in sialic acid may lead to a slight palliation of symptoms and perhaps a delay in the age of onset (30). Both of these unique traditional products of Sangesar presumably have high levels of sialic acid because of their preparation method. Although ‘Arshe’ and ‘Lour’ contain a high concentration of whey and are supposedly rich in sialic acid, neither of these dietary substances has been scientifically evaluated for their specific components. Further analyses are needed to quantify the percentage of sialic acid in each of these products. Hypothetically, the difference in the age of onset among five patients may be associated with the method of preparation and the level of consumption of ‘Arshe’ and ‘Lour’ (Table 1). On the other hand, the presence of HIBM or HIBM-like patients has not been reported in the past (i.e. in previous generations). Yet these milk-derived products have remained the primary food of the Sangesari people for decades, if not centuries according to the local community elders.

Additional research is warranted to determine if the absence of HIBM in the Sangesar people until recently can be attributed to a dietary-induced mitigating effect of sialic acid-containing milk products on HIBM pathophysiology, or instead, if the absence reflects physicians’ lack of clinical awareness of HIBM diagnostic criteria. More importantly, additional studies of other subpopulations of Iran will help clarify the true prevalence of HIBM in Iran.

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References

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