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Research Report

GNE Myopathy: Two Clusters with History and Several Founder Mutations

Zohar Argov* and Stella Mitrani Rosenbaum
Department of Neurology and the Goldyne Savad Institute of Gene Therapy, Hadassah -The Hebrew University Medical Center, Jerusalem, Israel

Abstract. GNE myopathy (previous names: HIBM, DMRV, IBM2) is a unique distal myopathy with quadriceps sparing. This recessively inherited myopathy has been diagnosed in various regions of the world with more than 150 disease-causing mutations already identified. Several of those are proven or suspected to be founder mutations in certain regional clusters and are described in this review. The review also discusses some historical aspects that might be relevant to the mutational distribution.

Keywords: Distal myopathy, GNE mutations, Roma/Gypsy, hereditary inclusion body myopathy, distal myopathy with rimmed vacuoles, ethnic clusters

INTRODUCTION

The first inclusive clinical description of what is today termed GNE myopathy appeared in 1984 in a special issue (foreschrift) of the Journal of Neurological Sciences honoring the departure of Lord Walton from Newcastle [1]. That phenotypic description noted the unique quadriceps sparing myopathy and identified the first (and still the largest) ethnic cluster of this disease in Jews originating from Iran (Persia). In the four decades since this description a lot of knowledge about the genetic basis of this myopathy has been gained, especially after the identification of the defective gene involved in this myopathy, UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase or GNE [2]. It became clear that this muscle disease (called for many years hereditary inclusion body myopathy or HIBM) is not limited to a single closed society. Furthermore, the identification of the gene led to the recognition that the distal myopathy with rimmed vacuoles (DMRV) described originally in Japan [3] is in fact the same muscle disorder [4]. Thus recently a group of investigators working for many years in the field suggested to term the condition GNE myopathy [5].

The current report reviews the world wide distribution of GNE myopathy which is unusual because in one large region of the world only a single homozygous mutation leads to the disease in the vast majority of patients while in other parts of the globe the variability of the mutations is very high (currently over 150 are known).

THE MIDDLE EASTERN CLUSTER OF GNE MYOPATHY

The first report of GNE myopathy was in a cluster of patients from Jewish descent originating from Iran. However, very quickly afterwards Jews from neighboring countries like Uzbekistan, Afghanistan, and Iraq were diagnosed to have this condition on clinical grounds (later confirmed by molecular genetics). This was not surprising as the Jewish communities in these countries originated from the ancient Persian Jewish community that was present in the region since the sixth century BC. Known historical persecution and natural expansion could explain such distribution. All

*Correspondence to: Prof Z. Argov, Department of Neurology, Hadassah University Hospital, Jerusalem 91120, Israel. Tel.: +972 2 6776938; Fax: +972 2 6437782; E-mail: zohara@ekmd.huji.ac.il.

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these patients are homozygous for the GNE mutation p.M743T. Furthermore, they all share a 700 kb haplotype in the region of GNE indicating a robust founder haplotype.

But in the recent 15 years this p.M743T mutation has been identified in Jewish clusters with less clear historical origin to the Persian Jews (e.g. Jewish families from Syria and Bukhara) and in Karaites from Egypt. The latter is an isolated sect that departed from main Judaism around the tenth century.

Even more surprising was the identification in Israel of several GNE myopathy patients of different Muslim Arabs families (of both Beduin and Palestinian origins) with the same homozygous mutation and haplotype. Thus, we reported that there is a Middle Eastern cluster of GNE myopathy [6] which we postulated to be at least 1300 years old (when Islam was created). Some unpublished data obtained by us have even dated this mutation to about 500BC.

The typical clinical features of GNE myopathy in its homozygous M743T form have been reported by us in the past [1, 6]. Now with more than 150 patients examined personally by one of us (ZA) in Israel and abroad over more than three decades the disease features of this cluster are well established. Onset is in early adulthood (third-fourth decade) with drop foot as the typical first sign (can be somewhat asymmetric at the onset). With progression the leg proximal musculature becomes affected (mainly the iliopsoas and hamstrings but also the gluteii) with marked preservation of the quadriceps power (this quadriceps sparing usually lasts through the disease course). The calf muscles (gatrocnemius mainly) may become weak at the early stages, but usually are affected later when the proximal musculature is markedly weak too. Upper limb involvement is usually delayed by at least a decade with proximal weakness that can involve the shoulder girdle being the first upper limb involvement. Distal weakness in the hands can also appear at this stage and some patients have marked long finger flexors weakness as the only distal involvement at this stage (reminiscent of the classical sporadic IBM sign). The neck muscles (mainly flexors) become affected in the last stages of the disease. There is no clinical cardiac involvement and respiratory insufficiency might only be a terminal feature of a bedridden patient. The progression rate is slow and patients lose their ambulation usually not before 10–15 years from onset and some maintain it for more than 25 years. Several of our patients reached the eight's decade of life, although they were very incapacitated.

There is some variability in the above description, mainly with age of onset that can be as early as 17 and as late as 48 years. Also, the rate of progression can more rapid (and even very fast in few) with early loss of ambulation. This usually occurs in those patients with marked involvement of the quadriceps from early stages (about 3–5% of affected individuals). There are few atypical presentations, the most important one is in patients who have onset in the proximal musculature of the legs without distal weakness. This was well recorded in two families and mimics other limb girdle syndromes. Mild facial weakness was seen only in few patients (most were from the Karaite families). There is one homozygous female who currently at age 78 years shows no weakness (her brother and niece are homozygous and affected). We have no explanation for the existence of such a non symptomatic homozygous subject.

More reports of GNE myopathy with the Middle Eastern mutation p.M743T came recently from even wider geographical area. Muslim families were described from Tunisia [7] and from other locations in the Persian Gulf region (e.g. Kuwait, as reported by Urtizberea et al at the Asian Oceanian Myology Congress, Bangkok March 2015). A cluster of GNE myopathy patients due to p.M743T mutation was identified in a small town (Sangesar) in Northern Iran. Many belong to the Bahai religion (a relatively new religion originating in Persia during the 19th century) [8]. Genetic studies in order to identify the common 'Middle Eastern haplotype' were not performed in these families, but we assume that it is identical.

Thus a regional founder mutation of GNE myopathy seems to exist in the Middle East and eastern part of North Africa, spanning through a large area from Iran to Tunisia. This founder mutation includes families belonging to two large (Jewish and Islam) and two small (Karaites and Bahai) religious groups. If indeed the suggestion of our unpublished data that this haplotype is 2500 years old is confirmed, can we explain this distribution? Historically, King Cyrus (named Koresh in Hebrew and Persian) ruled this whole area roughly from 560–530 BC. He allowed various deported peoples (including the Jews) to return to their relevant homelands and enlarged the trade in the region. This could be the time of initial spreading of this GNE founder mutation. Its presence in the smaller 'younger' religious group is probably derived from this original population; one could postulate cross marriage or rely on theories of the emergence of these religious sects from Judaism. The Sangegar cluster was postulated to arise from either intermarriage with members of a

close Jewish community or the religious conversion of regional inhabitants [8]. To date with the available data one can only speculate where exactly in old Iran/Persia did the M743T emerge.

THE ROMA/GYPSY GNE CLUSTER IN BULGARIA

A cluster of GNE myopathy patients with a previously described [2] mutation p.I618T was identified in Bulgaria [9]. Currently, there is no detailed report of this cluster but about 50 such patients were diagnosed, all are probably homozygous for this mutation, and all are of Roma/Gypsy origin. Most of their clinical features are within the common range of GNE myopathy phenotype, but there may be few unusual features in this cluster (e.g. onset in the hands). It seems not surprising that such a socially isolated community will harbor a recessive mutation that will be the founder of a cluster. In fact only in recent years has the Gypsy community of Bulgaria been recognized as a 'founder community', and few other neuromuscular disorders founder mutations have been identified in it [10].

The origin of the European Roma ethnicity is still debated [10] and its discussion is beyond the scope of this review. However, one of the leading theories is that this community originated in India and slowly spread from there to Eastern Europe, reaching it in the 13-14 centuries AD. Very interestingly, in the last (March 2015) Asian Oceanian Myology Congress in Bangkok, two groups from India have reported on their GNE mutation observations. Preethis-Kumar et al from Southern India described a common founder mutation (p.V727M) which was also found in other regions (Khadilker et al from Mumbai). However, the latter group has identified several native patients originating from Western India (Rajasthan) who were homozygous for p.I618T, the founder mutation in the Roma cluster. It is tempting to speculate that such a finding supports the theory of the origin of the Roma/Gypsies of Bulgaria being Western India and not the more distant Southern India region. More research is of course needed to identify a common haplotype between the two clusters to confirm this hypothesis, although such observation cannot settle the social science debate.

FOUNDER MUTATIONS IN OTHER COUNTRIES

The number of patients with GNE myopathy identified in Japan is higher than that reported from the large Middle Eastern clusters (totaling more than 200). Given its country origin an island with historical periods of isolation, one would expect to find a clear community founder mutation. Yet the genotypic profile of GNE myopathy in Japan is much more heterogeneous [11]. Numerous mutations have been described and a large fraction of the patients are compound heterozygotes. Among the identified mutations, two are more common: p.V603Land p.D207V [12]. The p.V603L mutation was also identified in neighboring countries (Korea and Northern China). This mutation seems to be a founder mutation for the region, or at least for Japan. Two more mutations were reported with higher frequency in Asian countries: p.A662V in South East Asia and the already mentioned p.V727M in Southern India (which was reported in Thailand and Malaysia). These mutations may be of a founder nature in these regions but more formal studies are needed to confirm it.

Another potential founder mutation (p.A409T) was described in a cohort of GNE myopathy patients from the British Islands [13]. Most of the patients harboring it were from north UK (Scotland and Ireland). Patients from other UK regions carried other mutations, some uniquely reported and some found also in other countries around the world.

SUMMARY

GNE myopathy is relatively easy to identify clinically with its unique distal onset and quadriceps sparing. With increasing recognition, more patients are diagnosed in different countries (at time in remote regions). The epidemiology of this myopathy is of special interest since there seems to be a paradoxical distribution: a geographically large diversified (ethnically and religiously) region has a clear founder mutation (and most probably a clear founder haplotype). Its historical origin and spread is intriguing. On the other hand a more potentially isolated and clearly localized country with a relatively high prevalence of the disease (Japan) displays highly diversified mutations. Additional potential founder mutations may contribute to the evaluation of historical migration of peoples. The list of currently identified founder mutations (Table 1) may be increased in the future when more GNE clusters will be identified.

Table 1
List of founder (first 3) and potential founder GNE mutations causing a myopathy

GNE mutation	Geographical area
M743T	Middle East & North Afrika
I618T	Bulgaria (Roma/Gypsy community)
V603L	Japan
D207V	Japan
A662V	East Asia
A409T	Northern UK

REFERENCES

[1] Argov Z, Yarom R. Rimmed vacuole myopathy sparing the quadriceps - A unique disorder in Iranian Jews. J Neurol Sci. 1984;64:33-43.

[2] Eisenberg I, Avidan N, Potikha T, Hochner H, Chen M, Olender T, Barash M, Shemesh M, Sadeh M, Grabov-Nardini G, Shmilevich I, Friedmann A, Karpati G, Bradley WG, Baumbach L, Lancet D, Asher EB, Beckmann JS, Argov Z, Mitrani-Rosenbaum S. The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. Nat Genet. 2001;29:83-7.

[3] Nonaka I, Sunohara N, Ishiura S, Satoyoshi E. Familial distal myopathy with rimmed vacuole and lamellar (myeloid) body formation. J Neurol Sci. 1981;51:141-55.

[4] Nishino I, Noguchi S, Murayama K, Driss A, Sugie K, Oya Y, Nagata T, Chida K, Takahashi T, Takusa Y, Ohi T, Nishimiya J, Sunohara N, Ciafaloni E, Kawai M, Aoki M, Nonaka I. Distal myopathy with rimmed vacuoles is allelic to hereditary inclusion body myopathy. Neurology. 2002;59:1689-93.

[5] Huizing M, Carrillo-Carrasco N, Malicdan MC, Noguchi S, Gahl WA, Mitrani-Rosenbaum S, Argov Z, Nishino I: GNE myopathy: New name and new mutation nomenclature. Neuromuscul Disord. 2014;24:387-9.

[6] Argov Z, Eisenberg I, Grabov–Nardini G, Sadeh M, Wirguin I, Soffer D, Mitrani-Rosenbaum S: Hereditary inclusion body myopathy: The middle eastern genetic cluster. Neurology. 2003; 60:1519-23.

[7] Amouri R, Driss A, Murayama K, Kefi M, Nishino I, Hentati F. Allelic heterogeneity of GNE gene mutation in two Tunisian families with autosomal recessive inclusion body myopathy. Neuromscul Disord. 2005;15:361-3.

[8] Khademian H, Mehravar E, Urtizberea JA, Sagoo S, Sandoval L, Carbajo R, Darvish B, Valles-Ayoub Y, Darvish D. Prevalence of GNE p.M712T and hereditary inclusion body myopathy in Sangesar population of Northern Iran. Clin Genet. 2012;84:589-92.

[9] Kalaydjieva L, Lochmuller H, Tournev I, Baas F, Beres J, Colomer J, Guergueltcheva V, Hermann R, Karcagi V, King R, Miyata T, Mullner-Eidenbock A, Okuda T, Milic Rasic V, Santos M, Talim B, Vilchez J, Walter M, Urtizberea A, Merlini L. 125th ENMC International Workshop: Neuromuscular disorders in the Roma (Gypsy) population. Neuromuscul Disord. 2005;15:65-71.

[10] Kalaydjieva L, Morar B, Chaix R, Tang H. A newly discovered founder population: The Roma/Gypsies. BioEssays. 2005;27:1084-94.

[11] Cho A, Hayashi YK, Momma K, Oya Y, Noguchi S, Nonaka I, Nishino I. Mutation profile of the GNE gene in Japanese patients with distal myopathy with rimmed vacuoles (GNE myopathy). J Neurol Neurosurg Psych Psychiatry. 2014;85:914-7.

[12] Nishino I, Carrillo-Carrasco N, Argov Z: GNE myopathy: Current update and future therapy. J Neurol Neurosurg Psychiatry. 2015; 86:385-92.

[13] Chaouch A, Brennan KM, Hudson J, Longman C, McConville J, Morrison PJ, Farrugia ME, Petty R, Stewart W, Norwood F, Horvath R, Chinnery PF, Costigan D, Winer J, Polivikoski T, Healy E, Sarkozy A, Evangalista T, Pogoryelova), Eagle M, Bushby K, Straub V, Lochmuller H. Two recurrent mutations are associated with GNE myopathy in the North of Britain. J Neurol Neurosurg Psychiatry. 2014;85:1359-65.