Letter to the Editor

Mutational analysis of PMP22, GJB1 and MPZ in Greek Charcot–Marie–Tooth type 1 neuropathy patients

To the Editor:

Charcot–Marie–Tooth type 1 (CMT1), the most frequent hereditary peripheral neuropathy, is characterized by marked clinical and genetic heterogeneity (1). Mutations in genes coding for peripheral myelin protein 22 (PMP22; MIM 601097), myelin protein zero (MPZ/P0; MIM 159440) and connexin 32 or gap junction beta 1 (Cx32/GJB1; MIM 304040) cause CMT1A, CMT1B and CMTX, the most common types of CMT1 (1). The objective of this study was to estimate the frequencies of the 1.5-Mb CMT1A duplication and of mutations in GJB1 and MPZ, in Greek CMT1 patients.

Patients and methods

Index cases with possible CMT1 diagnosis from 243 Greek families were included in this study. All patients underwent neurological examination, laboratory investigations to exclude acquired causes of demyelinating neuropathy and electrophysiological determination. Only patients fulfilling the diagnostic criteria of CMT1 were included, all of them with median MCV < 40 m/s (2, 3). The mean median MCV of the cohort was 26.2 ± 7.9 m/s. One hundred eighty-three cases were familial and 60 non-familial (51 sporadic and 9 isolated). Informed consent was obtained from all participants.

The presence or absence of the 1.5-Mb CMT1A duplication was detected using the long PCR method (4). The coding regions of GJB1 and MPZ genes were analyzed by sequencing (5, 6). Restriction enzyme digestion with MspI was used to confirm the absence of the novel GJB1 mutation (c.42-43insT) in 100 healthy controls. Statistical significance was tested using the χ² test.

Results and discussion

The duplication frequency in the entire sample was 25.9%. In familial cases the duplication frequency was 30.6% (56/183) and in non-familial cases 11.6% (7/60). These frequencies were significantly lower than those reported in most other population studies, which, despite different recruitment strategies and testing protocols, have detected similar CMT1A duplication frequencies. Our results, however, are closer to frequencies reported in population studies from Japan, Turkey and Norway (Table 1) as well as some populations (Spain, Sweden) included in the European collaborative study (7).

It is important to note that the methodology used to detect the CMT1A duplication (long PCR method) has an estimated sensitivity of 84–87% (8, 9). Although this may lead to an underestimation of the duplication frequency, the overall impact is likely to be small and should not alter our main conclusion, placing Greece in the countries with low relative frequency of CMT1A.

The frequency of CMT1A duplication is reported to be higher in familial than in non-familial cases. Thus the number of non-familial cases could be a parameter reducing the CMT1A frequency. However, our sample has a similar frequency of non-familial cases to several other studies with higher CMT1A duplication frequencies (7, 10, 11, 12). Therefore, we do not consider that the low CMT1A duplication frequency observed is as a result of the amount of non-familial cases in our sample.

The median MCV criterion used in the present study (<40 m/s) is slightly higher and more permissive than the more commonly used value of <38 m/s. However, it has been used before with no deleterious impact on overall CMT1A duplication frequency (3). Furthermore, other studies using even more permissive criteria (<50 m/s or <42 m/s) have reported high duplication rates of 60–80% (10, 13). Nevertheless, this criterion, along with the possible existence of autosomal recessive or misdiagnosed cases in our cohort, could partly contribute to the low CMT1A
duplication frequency observed. It should be noted, however, that obvious consanguineous marriages were not present in our cohort.

In conclusion, our results suggest a low relative CMT1A duplication frequency in the Greek population. This may imply a special genetic characteristic of Greeks, possibly resulting from relative genetic isolation (14). Given the low relative CMT1A duplication frequency also observed in the Turkish population, it would be worthwhile further investigating whether a low CMT1A prevalence characterizes the Eastern Mediterranean populations in general. Another possibility could be that the overall prevalence of the duplication is in fact not different from most studies, but that the relative frequency falls because of the existence of another unidentified mutation present at a higher rate in the Greek and/or Turkish population.

One hundred forty-five unrelated patients were further analyzed for mutations in the GJB1 coding region. Ten different GJB1 pathogenic mutations were detected in 12 index cases (Table 2). One of these, the c.42-43insT (Asn14fs), is a novel mutation that is described for the first time in this report. The T insertion provokes a frameshift mutation at the protein’s amino terminus creating a stop codon at codon 83. This mutation produces a truncated protein reportedly reducing the efficiency of hemichannel assembly (15, 16). Interestingly, this mutation resulted in a mild phenotype, although it created a severely truncated protein.

The frequency of mutations in the GJB1 gene in CMT1 patients in the Greek population (4.9%) was similar to frequencies reported in other ethnic populations (Table 1).

Out of the remaining cohort of 170 patients, a total of 99 patients were screened for mutations in the MPZ gene. One patient was identified with MPZ mutation (17). The overall frequency of MPZ mutation was 0.58%. This is the lowest frequency observed to date (Table 1). However, the very low number of cases precludes reliable statistical comparison with other populations.

In conclusion, the results of this study indicated that in the Greek population the duplication of PMP22 gene is the most common cause of CMT1,
among the genes studied, with a relative frequency that is significantly lower than in most other ethnic groups.

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