Short Report

Huntington’s disease in Greece: the experience of 14 years


A large scale genetic and epidemiological study of Huntington’s disease (HD) was carried out in Greece from January 1995 to December 2008. Diagnostic testing was carried out in 461 symptomatic individuals, while 256 were tested for presymptomatic purposes. The diagnosis of HD with a CAG expansion $\geq 36$ was confirmed in 278 symptomatic individuals. The prevalence of HD in Greece was estimated at approximately 2.5 to 5.4:100,000, while the mean minimum incidence was estimated at 2.2 to 4.4 per million per year. The molecular diagnosis of HD was confirmed in the majority of patients (84.4%) sent for confirmation. The false-positive cases 15.6% were characterized by the absence of a family history of HD and the presence of an atypical clinical picture. The uptake of predictive testing for HD was 8.6%. A prenatal test was requested in six pregnancies. The findings of our study do not differ significantly from those of similar studies from other European countries despite the relative genetic isolation of Greece. Of interest is the identification of clusters of HD in Greece. The presence or absence of a family history of HD should be interpreted cautiously, during the diagnostic process.

Conflict of interest

The authors declare no conflict of interest.

Huntington’s disease (HD) is an autosomal-dominant neurodegenerative disorder, characterized by choreic movements, cognitive decline and psychiatric disturbances. Despite the relative genetic isolation of the Greek population (1), a large-scale genetic and epidemiological study of HD in Greece is lacking.

The aim of this prospective study was to determine the demographic, clinical, epidemiological and molecular genetics features of HD in Greece from 1995 to 2008.

Subjects and methods

Our Neurogenetics Unit is the only laboratory of its kind in Greece. A total of 717 consecutive individuals, originating from various regions of Greece, were evaluated in person by the same neurologist of the Unit, after informed consent, during the period from January 1995 to December 2008. The evaluation included the Unified HD Rating Scale. In 11 bedridden patients, the full questionnaire was completed by the attending physician. In addition, a prenatal diagnosis was performed in six pregnancies.

Onset was defined as the age at which hyperkinesias, psychiatric symptoms or cognitive decline were first noticed.

The family history was considered positive when at least one of the family member had an established diagnosis of HD.

The CAG repeat number was determined according to Warner et al. (2) and the CAG

Key words: epidemiology – Greece – Huntington’s disease – neurogenetic – population

Corresponding author: Marios Panas, Department of Neurology, Neurogenetics Unit, Eginition Hospital, University of Athens, Athens, Greece, and Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Received 2 September 2010, revised and accepted 23 November 2010
expansion in the ATN1 gene, characteristic of dentatorubral–pallidoluysian atrophy (DRPLA), according to Vuillaume et al. (3).

Data were analyzed using the $\chi^2$ and Student’s $t$-tests and linear regression analysis. A value of $p < 0.05$ was considered statistically significant.

**Results**

The total number of requests per year, after an initial peak in 1995, increased till 2004 and gradually decreased till 2008. Demographic and genetic test results are shown in Table 1.

### Diagnostic testing

The diagnosis of HD was confirmed in 278/461 (60.3%) symptomatic individuals. The group molecularly excluded for HD was characterized by a significantly higher number ($p = 0.000$) of women, an earlier age at request ($p = 0.000$) and an earlier age at onset ($p = 0.000$) of their non-HD disorder.

### Prevalence

The number of patients studied probably reflects an under-ascertainment. However, the number of diagnoses increased over the first 8 years, stabilized in 2005 and showed a decrease till 2008, indicating that we may be approaching a nearly complete ascertainment of families. Thus, the prevalence of HD in Greece (with a population of 10,964,020) may be approximately 2.5:100,000.

A more accurate estimation could be 5.4:100,000, if 316 relatives with a clinical diagnosis of HD, who for various reasons had not been consented to DNA testing, are added.

The average test-positive (CAG $\geq 36$) rate (number of tests per million individuals in a given population per year) in Greece was approximately 1.6.

### Incidence

Bearing in mind that the ascertainment of our cases is incomplete, the mean minimum incidence rates of HD in Greece (including 32 patients who underwent pre-symptomatic testing and became symptomatic within the study period) could be estimated at 2.2/million/year. This estimation could reach 4.4/million/year if the 316 additional clinically ascertained HD patients were included.

### Family history

A positive family history of HD was present in 224 patients (80.5%) with CAG $\geq 36$ and in 31 (16.9%) with CAG < 36, while 147 patients (80.3%) with CAG < 36 and 16 patients (5.8%) with CAG $\geq 36$ had no family history ($p = 0.000$, Table 2).

In the group of patients with CAG $\geq 36$, a significantly higher age at referral ($p = 0.03$) and

---

**Table 1. Demographic and genotypic test results for Huntington’s disease**

<table>
<thead>
<tr>
<th>Total Gender</th>
<th>Age at request</th>
<th>Age at onset</th>
<th>CAGn</th>
</tr>
</thead>
<tbody>
<tr>
<td>M = 339</td>
<td>43.5 ± 16.7 (1–83)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F = 378</td>
<td>43.1 ± 17.1 (7–83)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diagnostic testing M = 223</td>
<td>48.3 ± 15.6 (3–83)</td>
<td>40.5 ± 15.4 (2–75)</td>
<td>36.6 ± 13.8 (12–94)</td>
</tr>
<tr>
<td>F = 238</td>
<td>48.7 ± 16.4 (7–83)</td>
<td>41.0 ± 16.2 (2–73)</td>
<td>34.0 ± 13.2 (15–92)</td>
</tr>
<tr>
<td>CAG $\geq 36$ M = 145</td>
<td>50.8 ± 14.3 (7–83)</td>
<td>44.2 ± 12.9 (3–73)</td>
<td>45.3 ± 6.7 (36–94)</td>
</tr>
<tr>
<td>F = 133</td>
<td>51.9 ± 14.4 (7–83)</td>
<td>44.5 ± 12.9 (6–71)</td>
<td>44.8 ± 6 (36–92)</td>
</tr>
<tr>
<td>CAG $&lt; 36$ M = 78</td>
<td>45.1 ± 18.1 (6–83)</td>
<td>37.7 ± 18.3 (2–75)</td>
<td>—</td>
</tr>
<tr>
<td>F = 105</td>
<td>46.6 ± 17.9 (7–79)</td>
<td>36.4 ± 18.6 (2–73)</td>
<td>—</td>
</tr>
<tr>
<td>Predictive testing M = 116</td>
<td>33.8 ± 19 (91–81)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F = 140</td>
<td>34.1 ± 14.8 (1–81)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CAG $\geq 36$ M = 54</td>
<td>31.5 ± 13 (1–72)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F = 69</td>
<td>30.9 ± 12.8 (1–62)</td>
<td>—</td>
<td>44.2 ± 4.1 (36–56)</td>
</tr>
<tr>
<td>CAG $&lt; 36$ M = 62</td>
<td>35.7 ± 14.8 (13–81)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F = 71</td>
<td>37.7 ± 13.9 (13–73)</td>
<td>—</td>
<td>20.7 ± 4.6 (14–35)</td>
</tr>
</tbody>
</table>

F, female; M, male.
Table 2. Demographics of referrals for HD and family history of HD according to test results

<table>
<thead>
<tr>
<th>Family history</th>
<th>Patients with a strong suspicion for HD</th>
<th>Patients with a doubtful diagnosis of HD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD confirmed (≥36 CAGs)</td>
<td>HD excluded (&lt;36 CAGs)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>248 (84.4)</td>
<td>46 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>217 (93.1)</td>
<td>16 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (26.8)</td>
<td>30 (73.2)</td>
<td></td>
</tr>
<tr>
<td>Known</td>
<td>20 (100)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

HD, Huntington’s disease.

Table 3. Family history of patients with CAGn ≥ 36 in relation to sex, age at referral, age at onset and CAGn

<table>
<thead>
<tr>
<th>Family history of patients with CAGn ≥ 36</th>
<th>Males</th>
<th>Females</th>
<th>Age at referral, mean ± SD (range)</th>
<th>Age at onset, mean ± SD (range)</th>
<th>CAGn, mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>117</td>
<td>107</td>
<td>49.1 ± 14 (7–78)</td>
<td>42.6 ± 12.9 (3–73)</td>
<td>45.3 ± 6.7 (36–94)</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>8</td>
<td>56.8 ± 10.9 (36–73)</td>
<td>50.1 ± 10.6 (32–71)</td>
<td>43.5 ± 3 (32–50)</td>
</tr>
</tbody>
</table>

In eight subjects (3.1%), the prior risk was unknown (no information about the affected relative). The mean age of these patients was 53.8 ± 16 years, significantly higher ($p = 0.001$) than the mean age of the two previous groups.

The transmitting parent in the group of 123 carriers was the father in 37 (30%) and the mother in 80 (65%) cases ($p = 0.000$).

Among the 256 individuals, 21 were children with a mean age at request of 13.2 ± 4.9 years (range 1–17). Carriers of the mutation (CAGn ≥ 36) were 11 children with a CAG size of 47.7 ± 4.9 (range 40–57).

The uptake of the predicting test for HD was estimated by the number of the unaffected family members aged over 18 years (the legal age of maturity in Greece) who, having being informed by the patient or the family physician, contacted our unit. Genetic counseling was structured as an initial information session, a second session in which blood was drawn for testing, and a results session.

Among the 256 individuals at risk, 235 were adults. The expected number of individuals at risk for HD, with an estimate of five at risk individuals for every patient (Conneally’s ratio 1:5) (4), was 2726. The overall uptake for predictive testing in this study represents approximately 8.6% of the at-risk HD population.

A prenatal test was requested by only six adult subjects. The parents were aware carriers. All prenatal tests were normal.

Geographic distribution

The region of origin was known in 218 unrelated molecularly confirmed HD families. The
mean number of these families was four per prefecture (administrative department). Clusters of HD families were identified in the Mani Peninsula ($p = 0.000$), prefecture of Messinia ($p = 0.000$), Cyclades islands ($p = 0.000$) and prefecture of Lasithi (island of Crete) ($p = 0.000$). Clustering was determined by comparing the observed to the expected frequency of HD unrelated families in any particular region, taking into account the population density.

Discussion

This report is the first large-scale attempt to study HD in Greece. The diagnosis of HD was confirmed in 60.3% of the patients. This percentage, as well as the size of the expanded allele repeats, the correlation between age at onset and (CAG)n size ($r^2 = 0.57$), the mean age at request, the mean age at onset and the mean CAGn, was similar to those of other studies (5–9).

The group genetically excluded for HD comprised mostly females, with an earlier age at request and an earlier age at onset, a finding that confirms the observation of Almqvist et al. (6), who reported only a trend for significance. The absence of family history and the presence of atypical clinical symptoms in this group emphasize the importance of these data for the diagnosis of HD.

The negative family history of HD observed in 16/278 genetically confirmed HD patients could be explained by new mutations, misdiagnosis in family members, non-penetrance, or non-paternity. Other authors report significantly lower (6, 10) or similar (11) percentages. These discrepancies are probably because of differences in the ascertainment of the family history.

Surprisingly, 16.9% of our patients with CAGn <36 had a positive family history, a percentage significantly higher than the one reported by other authors (6, 10, 11). This difference is probably because of the fact that a number of patients were referred to our Unit by non-neurologists. The detailed clinical investigation and follow-up of these patients revealed a misdiagnosis (e.g. Parkinson’s disease, essential tremor, dystonia, dementia, depression, etc.). Three patients with a positive family history and typical symptomatology of HD (HD-like) could represent a clinical phenocopy of HD. Prior to the identification of the HD mutation, the initial diagnosis in these patients would obviously be HD.

The false-positive group was characterized by the absence of a family history of HD and the presence of atypical clinical signs and symptoms in the majority of cases.

These observations highlight the relative diagnostic value of the family history as well as the importance of genotyping for the confirmation of the diagnosis in families with HD.

The calculated prevalence of 5.4/100,000 shows no major differences in comparison to other European populations, a finding that does not support the hypothesis of a lower frequency of HD in southern Europe (12).

The test-positive rate might be underestimated, because it is almost certain that there are subjects who became symptomatic during the study period but for various reasons were not subjected to mutation analysis.

The incidence of HD in Greece lies within the range reported for other Caucasian populations (6, 10, 13).

The significantly lower age at request in the 25% risk group is probably because of the lack of a first-degree relative.

The significantly higher age at request in the unknown prior risk group is probably reflecting the lack of information concerning the affected relative, as well as the tendency to avoid the idea of a possible transmission of the disease to offspring.

The greater percentage of mothers as transmitting parents in the group of carriers could not be plausibly explained on biological or sociocultural ground. Furthermore, this finding was not replicated in the group of molecularly confirmed HD patients.

The decrease in the number of diagnoses during the last few years of the study probably reflects the fact that the majority of those expected to undergo predictive testing had already been examined. Preliminary data from 2009 seem to be in accordance with this hypothesis. Another explanation could be the disappointment because of the lack of an effective treatment.

The low uptake observed in our study (14–16) could be explained in part by the particular geographical characteristics of Greece, the method of calculation of the expected number of individuals at risk, the hesitation to discover one’s status regarding HD, the lack of information about predictive testing, or the hope of a future therapy.

According to recommendations, predictive testing for HD in asymptomatic children should be deferred until the age of majority (17). However, opposing views have been expressed (18). During the 1995–2000 period, exclusively under very special circumstances (disruptive anxiety and uncertainty of the healthy parent significantly influencing the child, cases of young people near the age of maturity with a high level of social
and psychological development), our unit adopted the practice of testing asymptomatic children aged <18 years, provided that the results would be announced only to the child at the age of majority.

This study adds to the evidence included in the European collaborative study for prenatal testing (19), increasing the number of prenatal tests in Greece to six. This is a small number, similar to those observed in other countries (14, 19). It is probably related to the hope for a future therapy of HD, the fear of social stigma, the religious beliefs against abortion, or the complete denial of child bearing.

The presence of HD clusters in Greece is not a surprise, given the relative genetic isolation of the Greek population and the particular geographical and cultural characteristics of the cluster regions.

In conclusion, the main characteristics of HD in Greece do not differ from those of other European countries. Findings of our study with potential importance are the relative contribution of the family history in the diagnosis of HD, the low test-positive rate, the low uptake of predictive tests, the small number of prenatal tests, and the presence of clusters. These data are essential for the design of an efficient prevention program for HD and the better organization of the National Health System in Greece.

References