LETTER

Incidence and prevalence of Huntington disease (HD) in the Sultanate of Oman: the first Middle East post-*HTT* service-based study

INTRODUCTION

Huntington disease (HD) is a neurodegenerative, dominantly inherited disorder, which may result in a debilitating movements disorder and cognitive decline with progressive loss of independence. HD frequency in the Middle East has never been defined after the *HTT* gene discovery and cases of HD have been reported only sporadically.[1]

In July 2013, Italian League for Research on Huntington Disease Foundation was contacted by a family from Oman, who reported to be affected by HD since many generations. Indeed, that family may represent the largest HD cluster ever described in the Middle East, owing to a high number of intermarriages and subsequent increase in mutation heritability risk. Given the gaps in our knowledge about HD in the Middle East, we took the opportunity to study and determine the incidence and prevalence of HD in this region.

SUBJECTS AND METHODS

We performed an observational, service based, study from August 2013 to March 2019 in the Muscat region, Sultanate of Oman. Prevalence was estimated on the number of affected and at-risk individuals, who were referred to the National Genetic Centre (NGC) of the Royal Hospital in Muscat, the main Ministry of Health Country health organisation. We are, therefore, confident to have an accurate representation of most HD cases and families who reside in this region. A priori risk, that is, the risk of disease associated with an individual at birth, was separated into groups: 50% risk (a first-degree relative is affected with or mutation-positive for HD), and >50% risk (an individual with both at-risk parents or one affected and one at-risk parent). All subjects were clinically evaluated by the Unified HD Rating Scale (UHDRS)[2] and examined by the same neurologist (FS) with expertise in HD. Clinical characteristics, including age at onset, age at death and symptoms presentation, were recorded based on first relevant neurological and psychiatric symptoms and according to either expert clinician assessment (affected alive patients) or retrospective recall via interviews with caregivers/family members (affected deceased patients) (online supplementary). Clinical diagnosis of HD was confirmed by direct examination of the subject or by careful re-examination of patients' files. Cases with suspicious clinical history were only included in the prevalence of at-risk individuals. The diagnosis of juvenile-onset HD (JoHD) was based on the appearance of the first neurological symptoms before age 20.[3] Once we identified a given family, we performed: (1) analysis of pedigrees with identification of resident family branches in Muscat region; (2) door-to-door interviews; (3) interview of patients and relatives; (4) interviews of physicians who may have gotten in touch to a given family.

Genetic analyses to determine CAG repeat length in the *HTT* gene were performed in parallel at the NGC in Muscat, Sultanate of Oman and at the CSS-Mendel Institute, the Roman branch of IRCCS Casa Sollievo della Sofferenza (CSS) Research Hospital, after the patients signed informed consent as previously described.[3]

RESULTS

The Omani cohort comprised 392 individuals (129 males, 133 females and 130 missing data for gender), from four unrelated families, 67 of whom—41 (61.2%) alive and 26 (38.8%) deceased—were affected by HD (mean population age=46.6 years; mean age at onset=34.5 years, mean CAG repeat length=48.3). Nine out of 67 patients (13.4%) manifested with joHD (figure 1A). The remaining 325 individuals (82.9%) were at risk for HD. Sixty-six (20.3%) carried a risk above 50%, 64 of which (96.9%)

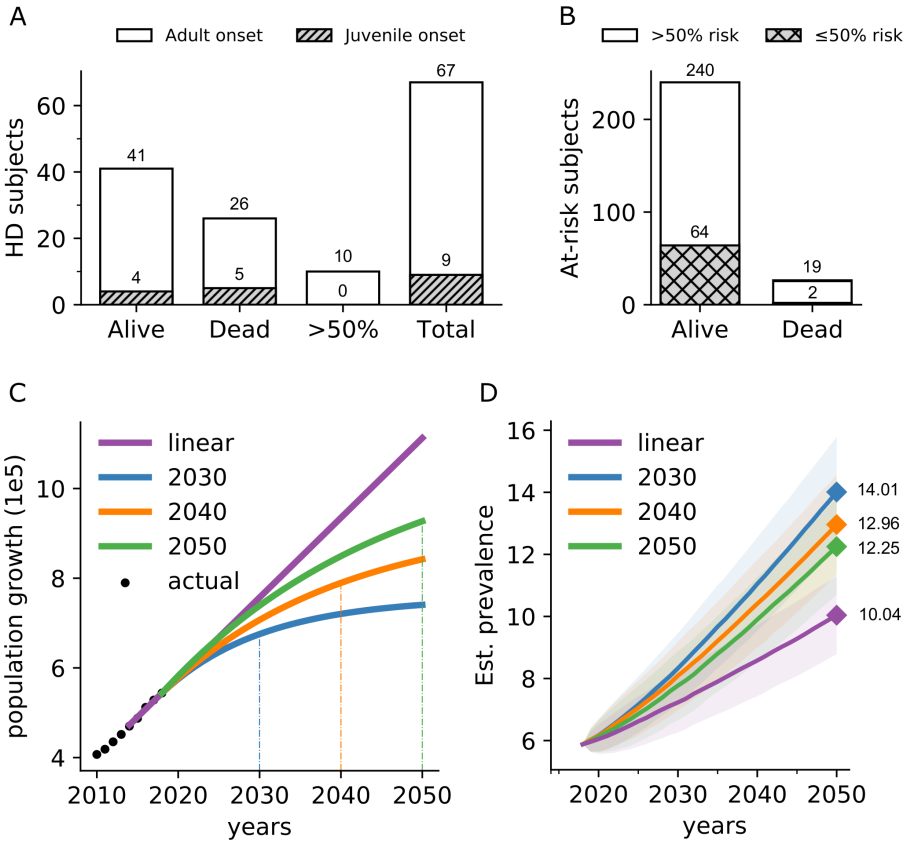

Figure 1 (A) Frequency of symptomatic and at risk individuals living in the Muscat region, Sultanate of Oman, Middle East and prevalence estimates of HD until 2050. (A) Vital status of patients with adult onset and joHD. A fraction of adult-onset patients, but not of joHD, had a risk beyond 50% to inherit a CAG mutation from parents due to more than one at-risk parent, that is, two at-risk parents, one at-risk and one affected or both affected. (B) Proportions of patients stratified by vital status and risk. (C) Simulations of the Muscat population growth, which fit actual data from 2010 to 2018 and then evolve linearly or exponentially over time, with an inflection at 2030, 2040 or 2050. (D) Monte-Carlo HD prevalence estimate for the period 2018–2050. Dots mark the prevalence predictions in 2050, based on the estimated population in the Muscat region computed by one of the four growth models. joHD, juvenile-onset HD; HD, Huntington disease.

are now alive while 2 (3.1%) are deceased; 259 (79.7%) carried a risk ≤50%, 240 of which (92.7%) are alive and 19 (7.3%) are deceased (figure 1B). Among the 41 alive patients, 28 received a genetic confirmation of the clinical diagnosis, while 13 of them, who refused the genetic test, were frankly symptomatic and clinically ascertained (ie, confidence level of 4 at the UHDRS).

The actual HD frequency was 41 alive patients and 304 at-risk alive individuals, among 556 731 inhabitants (from https://data.gov.om) living now in the Muscat region (ie, 7.36 per 100 000, 95% CIs 5.40 to 10.02 and 54.60 per 100 000, 95% CIs 48.79 to 61.10, respectively). Based on actual demographic data available from 2010 to 2019 and simulating the population growth using both linear and exponential models inflecting at 2030, 2040 and 2050 (figure 1C), we expect by discrete-time Markov chain analysis that prevalence will range from 10.04 to 14.01 per 100 000 in 2050, 95% CIs 8.36 to 12.12 to 11.58 to 17.03 (figure 1D), based on the value of HD incidence rate of 0.56 per 100 000, and a death rate of 2.27 per million (online supplementary data), which conservatively overestimates the Muscat death rate of 1.82 per million calculated on a limited number of Omani deceased patients. The 95% CIs were calculated using the Agresti-Coull method.

DISCUSSION

Our study provides the first conservative assessment of the frequency of HD in the Middle East, that is, in the Muscat region of the Sultanate of Oman. Our data report a prevalence estimate of 7.36 per 100 000 inhabitants (2019), which is in agreement with the average prevalence rate in Europe, North America and Australia, that is, 5–10 per 100 000,[4] and an estimate of net prevalence increase from 1.4-fold to 2-folds in 2050, under the assumption of a linear or exponential population growth and constant incidence/death rates. Moreover, our analysis highlights a particularly high joHD frequency (13.4% of all HD cases), one of the largest so far described.[5]

Given that the Portuguese haven been ruling Muscat and coastal Oman in the 17th and 18th centuries, it is possible that Europeans introduced the disease into this Country, in the heart of the Arabic peninsula and from there the disease widespread in other Middle Eastern areas. It is also possible that new mutations may have arisen in specific haplogroups. However, our study ascertains that HD spread into the Middle East with a frequency similar to Caucasian populations. Considering the conservative estimate of prevalence, we inferred for the Sultanate of Oman for the next 30 years, our study suggests that the global number of HD and joHD subjects is consistently larger than so far reported.

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