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Short Report

Epidemiology of Huntington disease: first post-*HTT* gene analysis of prevalence in Italy

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Huntington disease (HD) prevalence shows geographic variability and has been recently updated by taking into account the mutation diagnostic test. In Italy, the last epidemiological estimation was reported well before the *HTT* gene discovery and the availability of the corresponding genetic test. It reported a prevalence of affected subjects ranging between 2.3 and 4.8/100,000 in some restricted areas of Northern Italy. We have performed a service-based epidemiological analysis in a very restricted geographic area named Molise, where our institutions currently operate and represent the only point of reference for rare neuropsychiatric diseases. The estimated prevalence rate found was 10.85/100,000 (95% confidence interval (CI): 7.20–14.50), remarkably higher than that previously described before the gene test analysis was available, and expected to an increase of an additional 17% by 2030, because of Italian population aging. According to our analysis, we estimate that about 6500 subjects are currently affected by HD in Italy, and that this number will further increase in the next decades because of population aging, variable phenotype penetrance and improved life expectancy.

Conflict of interest

The authors declare that no competing interests exist.

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Huntington disease (HD) prevalence rate varies among different populations, with those of European ancestries showing highest, likely underestimated, rates (1). Epidemiological analyses on hereditary rare diseases, such as HD, are required to determine the frequency and distribution of HD mutation carriers. They should also investigate the influence of environmental or biological factors or on both patients' phenotype and prevalence rates in different geographical areas. *HTT* gene discovery opened a new era in the identification of mutation carriers by direct mutation test, thus disclosing new precise prevalence around the world (2). In Italy, the last analysis of prevalence, which was conducted well before the *HTT* gene discovery and creation of the corresponding genetic test, reported a prevalence rate of affected subjects ranging between 1.8 and 4.8/100,000 in some restricted areas of Northern Italy (3, 4). Molise region, where our institutions currently operate representing the only point of reference for rare neuropsychiatric diseases, has been granted a measure of political and administrative autonomy since 1970. Because this is among the most geographically restricted areas in Italy, such administrative setting allows epidemiological analyses to be realistic.

We performed a service-based study of the HD prevalence in this area and provided a theoretical prediction of the expected rate in the coming years, based on the expected population aging.

Methods

Italian League for Research on Huntington and related diseases (LIRH) Foundation, a site of the European HD Network as LIRH Rome, is a non-profit organization including HD families, researchers and physicians. LIRH

has set observational HD points in several parts of Italy since 2001, and has been collecting data and samples for research purposes (i.e. ENROLL-HD) from HD subjects originating from every part of the Country. It operates in collaboration with medical institutions, e.g. the Centre for Neurogenetics and Rare Diseases of Neurological Research Institute Neuromed, since 1998.Neuromed is included in the Italian Network for rare diseases, whose task is to set a national registry where HD shows a distinct code (i.e. RF0080). To date, data from about 800 HD subjects from a total of about 500 apparently unrelated families have been collected in our archives. Molise region hosts a population of 313,341 inhabitants as of December 2013 and represents the area where both our institutions (LIRH and Neuromed) operate as the only two centres of reference for neurological rare diseases. We are therefore confident to have an accurate representation of most HD cases and families who reside in the Molise region. *A priori* risk, 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 25% risk (a second-degree relative is affected with or mutation positive for HD). Asymptomatic mutation-positive individuals are pre-manifest, likely to develop HD in the future. Age at onset was determined by a neurologist expert in the field, according to neurological or significant psychiatric manifestations, as described (5). All subjects were evaluated using the Unified HD Rating Scale (UHDRS) (6). By analyzing all pedigrees, we conducted a systematic study to establish the number of patients as well as of those with an *a priori* 50% and 25% genetic risk. Once we identified a given family, we performed: (1) analysis of pedigrees with identification of resident family branches in Molise; (2) door-to-door interviews and telephone survey; (3) interview of patients and relatives; (4) interviews of physicians who may have gotten in touch to **a** given family; (5) hospital/clinic record review; (6) inquiry of families through questionnaires and web sites (www.lirh.it); and (7) administrative database reviews, as the regional rare disease registry.

This project including HD data collection, genetic testing program and collection of DNA samples for research purposes, was approved by the local ethical committee based at Neuromed. ENROLL-HD study was approved by Institutional Review Board (IRB) of Istituto Leonarda Vaccari, based in Rome. All subjects signed an informed consent before data and blood sample collection.

Statistical analysis was conducted using a commercially available statistical software package (JMP by SAS, http://www.jmp.com). The normality of all variables was assessed through the Kolgomorov–Smirnov test. Standard error and 95% CIs for estimates of prevalence and population at risk were calculated based on the assumption of Poisson's distribution. Correlation was assessed using the Spearman test (for CAG *vs* AO) and differences in prevalence rates between groups were evaluated by the Mann–Whitney (*U*-value) test. Statistical significance was considered when $p < 0.05$. To predict the expected variation in prevalence rate according to the aging of the Italian population until 2030, we split all subjects according to their status (50% risk and symptomatic) in diff erent classes of ages, in years (predicted age variation of the Italian population is reported in the web site: http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTHEALTHNUTRITIONANDPOPULATION/EXTDATASTATISTICSHNP/EXTHNPSTATS/0,,contentMDK:21737699 ~ menuPK:3385623 ~ pagePK:64168445 ~ piPK:64168309 ~ theSitePK:3237118,00.html). Statistical significance was considered to be achieved when $p < 0.05$.

Results

We have identified 31, apparently unrelated, HD families living in Molise with 34 patients showing a clinical diagnosis of HD. Twenty-six received genetic confirmation, while eight of them, who refused the genetic test, were clearly symptomatic and clinically ascertained (i.e. confidence level of 4 at the UHDRS), by the same neurologist with expertise of HD. These patients had affected, genetically confirmed, relatives. The estimated prevalence rate was 10.85/100,000 (95% CI: 7.20–14.50), with no significant gender difference (Fig. 1a). When considering all mutation carriers, including at-risk individuals who were positive to the predictive genetic test, we found a total of 42 individuals with an estimated prevalence rate of gene-positive subjects (affected plus pre-manifest subjects) of 13.40/100,000 (95% CI: 9.35–17.45) (Fig. 1a).

We found 280 living, at-risk (prevalence rate of 39.2/100,000, 95% CI: 37.4–41.0) subjects on family pedigrees, 124 in the 50% risk group and 156 in the 25% risk group, resulting in a prevalence rate of 39.57 (95% CI: 32.61–46.53) and 49.79 per 100,000 (95% CI: 41.98–57.60), respectively (Fig. 1b). By combining at-risk ($n = 280$) and affected ($n = 34$) people (total $n = 314$), we found that about 1/1,000 people in this area experienced HD, either because they had symptoms or because they were related to people with HD or at risk to develop HD.

Mean age of the patient's cohort was 63.6 ± 13.8 years. Mean age of neurological symptom onset was 49.04 ± 13.36 years. Non-zero age-specific prevalence rate of HD ranged from 4.35 per 100,000 aged 40 to 44, to 49.67 per 100,000 aged 65 to 69 years. Non-zero age-specific prevalence rate of *a priori* 50% risk subjects ranged from 8.40 to 69.67 per 100,000 (Fig. S1, Supporting Information). By taking into account the aging of the Italian population in our Country, we simulated the variation of the disease frequency, as expected by 2030. Our simulation indicated an additional 17% prevalence increase in symptomatic subjects in 2030, as compared with the present estimated HD prevalence . Conversely, the prevalence of 50% at-risk people is expected to decrease, because they will fall in the age class 40–55 years, whose reduction is expected in the coming years, likely due to the expected decreasing number of births (Fig. 2 and supplementary Fig. 1).

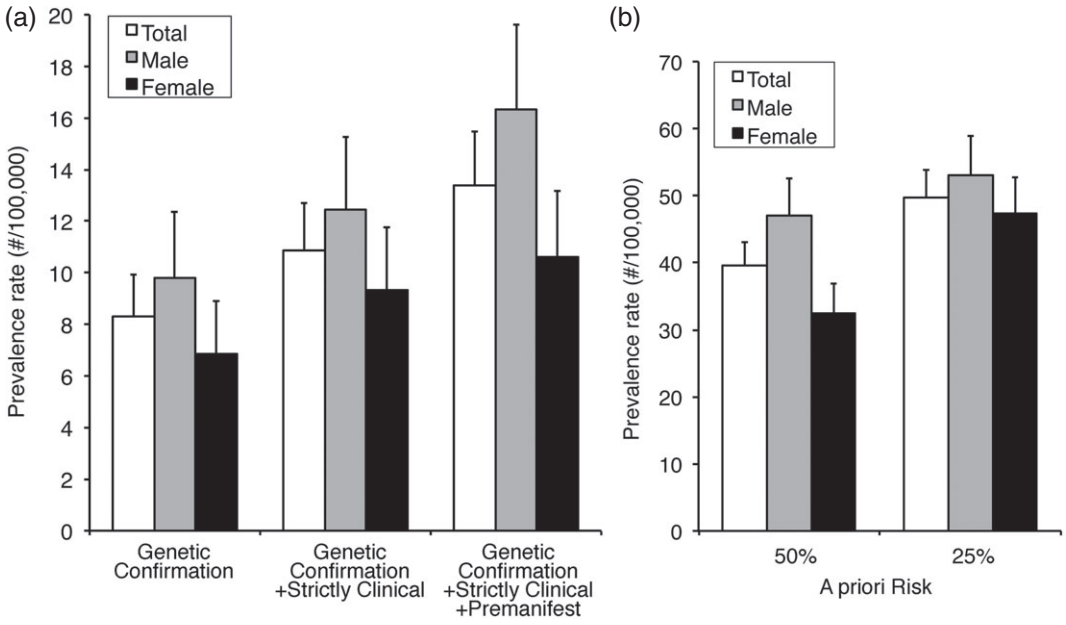

Fig. 1. Prevalence rate of Huntington disease. (**a**) Prevalence rate of symptomatic subjects and of symptomatic subjects plus unaffected mutation carriers (pre-manifest). (**b**). Prevalence rate of at-risk subjects.

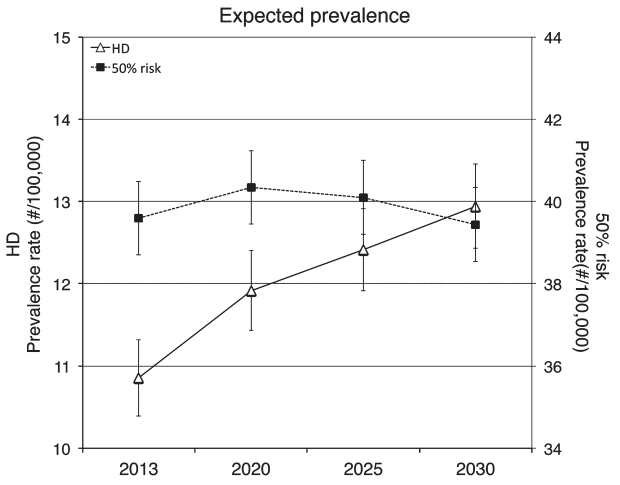

Fig. 2. Expected prevalence rate of Huntington disease symptomatic and at-risk subjects by 2030. The expected patients' prevalence is progressively expected to increase, because of the general population aging and life expectancy by 2030, according to the age variation in the Italian population.

Discussion

We report data from the first analysis of prevalence performed in an Italian population since the discovery of *HTT* gene. Our service-based study describes a prevalence rate substantially higher than previously reported. Many factors may contribute to explain the increase in HD prevalence observed in several populations in these last years, including improved life expectancy and more accurate diagnoses (2, 7). Indeed, a systematic prevalence meta-analysis indicated only half of studies performed after the gene test became available. Our study was conducted on a selected population resident in Molise, a small Italian region with about 300,000 inhabitants. We believe that our strategy allowed the screening of most HD families in this area, since the genetic test became available. A previous pre-*HTT* analysis on a population of similar size had been performed in 1990 by Pavoni et al., in a selected northern area of Italy, describing a HD prevalence of 1.85/100,000, a rate remarkably lower than that we detected (3). Most analyses performed on European ancestries did not surpass a prevalence of about 6/100,000. Morrison reported a prevalence of 10.6 (8), the highest in Europe, and predicted even higher HD frequency in UK because of improved life expectancy in the general population and prolonged life span in HD patients, likely due to improved therapeutic approaches (9). More recently, a prevalence ranging between 13.7 (in the general population) and 17.2 (in the Caucasian population) was also reported in Canada (1). Evans et al. described similar prevalence esteem in UK with highest rate of 15.8 in 51- to 60-year age range (9). Interestingly, we also detected the highest prevalence in a similar age class (i.e. 55- to 69-year age range) and presume that it will keep increasing an additional 17% in the coming years, owing to the expected aging and increased life expectancy of our population.

In our analysis, we found a prevalence rate of 10.85 per 100,000 that is more than double of what was reported in several other areas in Italy, before gene test became available. We are aware that our analysis has some limitations because of the cohort size studied. However, the small size of patients' cohort has been analyzed within one of the most restricted and well-studied geographical areas in the country and is, therefore, a strong representative of the true prevalence in our population. Moreover, we found that, by combining at-risk (50% and 25%, $n = 280$) and affected ($n = 34$) people (total $n = 314$), about 1/1000

people in this small area of Italy experienced HD, either because they had symptoms or because they were related to people with or at risk to develop HD. If extended to the whole Country, our esteem of prevalence indicates that there may be about 6500 HD patients in Italy. Considering the fact that data from about 1000 patients are included in the international HD registry (i.e. Euro-HD Network) from Italian sites, we conclude that an intense effort is needed to improve awareness of this disease in our Country.

In conclusion, because the Italian population is considered very heterogeneous, due to several historic influences from neighbor populations, the analysis of influence of environmental and genetic factors on HD frequency and phenotype variability (10) would be recommended. Moreover, the analysis of genetic factors variability within populations with heterogeneous ethnic backgrounds may offer clues to the application of new therapeutic technologies, hopefully in the near future (11).

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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