The Global Epidemiology of Hereditary Ataxia and Spastic Paraplegia: A Systematic Review of Prevalence Studies

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Key Words

Hereditary ataxia · Hereditary spastic paraplegia · Spinocerebellar ataxia · Prevalence · Systematic review · Meta-analysis

Abstract

Background: Hereditary cerebellar ataxias (HCA) and hereditary spastic paraplegias (HSP) are two groups of neurodegenerative disorders that usually present with progressive gait impairment, often leading to permanent disability. Advances in genetic research in the last decades have improved their diagnosis and brought new possibilities for prevention and future treatments. Still, there is great uncertainty regarding their global epidemiology. **Summary:** Our objective was to assess the global distribution and prevalence of HCA and HSP by a systematic review and meta-analysis of prevalence studies. The MEDLINE, ISI Web of Science and Scopus databases were searched (1983–2013) for studies performed in well-defined populations and geographical regions. Two independent reviewers assessed the studies and extracted data and predefined methodological parameters. Overall, 22 studies were included, reporting on 14,539 patients from 16 countries. Multisource population-based studies yielded higher prevalence values than studies based primarily on hospitals or genetic centres. The prevalence range of dominant HCA was 0.0–5.6/10⁵, with an average of 2.7/10⁵ (1.5–

4.0/10⁵). Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease was the most common dominant ataxia, followed by SCA2 and SCA6. The autosomal recessive (AR) HCA (AR-HCA) prevalence range was 0.0–7.2/10⁵, the average being 3.3/10⁵ (1.8–4.9/10⁵). Friedreich ataxia was the most frequent AR-HCA, followed by ataxia with oculomotor apraxia or ataxia-telangiectasia. The prevalence of autosomal dominant (AD) HSP (AD-HSP) ranged from 0.5 to 5.5/10⁵ and that of AR-HSP from 0.0 to 5.3/10⁵, with pooled averages of 1.8/10⁵ (95% CI: 1.0–2.7/10⁵) and 1.8/10⁵ (95% CI: 1.0–2.6/10⁵), respectively. The most common AD-HSP form in every population was spastic paraplegia, autosomal dominant, type 4 (SPG4), followed by SPG3A, while SPG11 was the most frequent AR-HSP, followed by SPG15. In population-based studies, the number of families without genetic diagnosis after systematic testing ranged from 33 to 92% in the AD-HCA group, and was 40–46% in the AR-HCA, 45–67% in the AD-HSP and 71–82% in the AR-HSP groups. **Key Messages:** Highly variable prevalence values for HCA and HSP are reported across the world. This variation reflects the different genetic make-up of the populations, but also methodological heterogeneity. Large areas of the world remain without prevalence studies. From the available data, we estimated that around 1:10,000 people are affected by HCA or HSP. In spite of advances in genetic research, most families in population-based series remain without identified genetic mutation after extensive testing.

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Introduction

Hereditary cerebellar ataxias (HCA) and hereditary spastic paraplegias (HSP) are two distinct groups of genetic neurodegenerative disorders. They usually present with progressive gait impairment, often leading to permanent disability and even premature death [1, 2]. Furthermore, there is some clinical overlap between them, especially in the forms with recessive inheritance. Consequently, they are often approached together in epidemiological studies. There have been historical difficulties in their diagnosis and classification [3, 4], reflected in heterogeneous inclusion and classification criteria used in the early epidemiological studies. A turning point, however, was the definition of diagnostic and classification criteria based primarily on the mode of genetic inheritance by Anita Harding in 1983 [5]. Furthermore, the development of genetic techniques in the last decades brought new possibilities for precise diagnosis and improved classification founded on genetic testing. Methods for preventing transmission to the next generation have become available [6, 7] and new therapeutic targets are being investigated [8, 9]. An increasing number of epidemiological studies have been performed in recent years. However, there is great uncertainty regarding their global distribution and prevalence.

To the best of our knowledge, only one systematic review was attempted in this field in order to assess the prevalence of HCA in the UK, though the authors could not find any study that suited their inclusion criteria [10]. A review on the population genetics and relative frequency of HCA mutations has recently been published [11], but it was not based on a systematic review of prevalence studies.

We aimed to describe the global distribution of HCA and HSP through a systematic review of studies reporting prevalence estimates in a defined population and to assess them using a framework of methodological parameters. While our primary goal was to present a descriptive and critical review of the selected studies, we also estimated pooled prevalence values by using random effects meta-analysis.

Methods

This systematic review was performed and reported following the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for systematic reviews of observational studies [12].

Search Strategy

We searched for studies published after 1983, when Harding's [5] diagnostic and classification criteria for HCA and HSP became widely used. A systematic search was performed on the MEDLINE, ISI Web of Science and Scopus databases between January 1983 and August 2013. The following search terms were used: 'cerebellar ataxia', 'spinocerebellar ataxia', 'spinocerebellar degeneration', 'hereditary ataxia', 'Strumpell-Lorrain', 'spastic paraplegia', 'hereditary spastic paraplegia', 'epidemiology' and 'prevalence'. The search queries can be consulted in online Appendix 1 (for all online supplemental material, see www.karger.com/doi/10.1159/000358801). Furthermore, the reference lists of the selected papers were examined for additional studies. The search was not restricted by language.

Study Selection

We selected studies providing a prevalence estimate for a defined population in a delimited geographical region for at least one of the following subgroups: autosomal dominant HCA (AD-HCA), autosomal dominant HCA (AD-HCA), autosomal recessive HCA (AR-HCA), AD-HSP or AR-HSP, X-linked HCA, X-linked HSP, HCA with mitochondrial inheritance or HSP with mitochondrial inheritance. Studies focusing on the prevalence of unique genotypes or phenotypes were excluded. Since we expected few publications, we defined broad inclusion criteria regarding the methodological approaches to identifying, diagnosing and classifying patients. Two independent investigators (L.R. and C.M.) reviewed the titles and abstracts of the publications identified by the initial search strategy. Studies that clearly did not meet the inclusion criteria were excluded, and the remaining studies were appraised as full-text papers. Inclusion was based on agreement between the two reviewers. In cases of non-consensus, a third independent review (by M.C.S.) was obtained for decision.

Data Collection and Methodological Assessment

Two reviewers (L.R. and C.M.) independently extracted relevant methodological parameters and epidemiological data from each study. A predefined form was used (online Appendix 2), which included the following parameters: study design, population, geographical area, time period, number of patients identified, patient ascertainment strategies, inclusion criteria, classification criteria, study limitations and prevalence estimates for each of the subgroups. When prevalence estimates were not reported separately for each group, we calculated them if the necessary data were provided in the paper. Prevalence is reported as the number of patients per 100,000 people. Regarding studies that included surveys by health professionals or health institutions as a source of patients, we present the prevalence estimates unadjusted for responding rates.

Studies were classified according to the main sources of information. We defined a study as multisource when overlapping patient-finding strategies were used to include patients from at least: (1) primary care or community settings; (2) hospital or equivalent specialized care; and (3) systematic investigation of the families of patients identified via the previous sources.

Quantitative Analysis

We performed a meta-analysis of the overall combined HCA and HSP prevalence and of the prevalence of the subgroups (AD-HCA, AR-HCA, AD-HSP and AR-HSP). In order to improve the homogeneity of the pooled data, we used the prevalence estimates without isolated patients (patients with negative family history and

Fig. 1. Flow chart of studies selected through the different phases of the systematic review.

no genetic diagnosis). Therefore, studies that did not exclude or did not report the number of isolated patients were excluded from the meta-analysis. Regional studies were excluded if national prevalence data were available. If more than one study was available for the same population, the most recent was selected. For the meta-analysis of each subgroup, we also excluded studies with a substantial number of patients not classified according to the mode of inheritance (>25%) and studies from which the subgroup prevalence could not be ascertained.

The meta-analysis was performed in Microsoft Excel for Macintosh 2011, using a prebuilt spreadsheet [13]. Since prevalence heterogeneity is expected from the different genetic backgrounds of the reported populations, we used a random-effects model to estimate the prevalence with a 95% CI. We present separate results for studies published only after 2000 as the recent developments in the field of genetics could improve patient identification and classification. Furthermore, a weighted linear regression analysis of the prevalence values was performed to detect time trends or effects of using different patient ascertainment sources. Since many studies spanned several years, the middle year of fieldwork was used for the analysis. The effect of each source (hospital records, general practitioner survey, registries, genetic centre records and investigation of probands' families) was analysed separately. SPSS version 21.0 was used, considering a two-sided 0.05 significance level.

Results

We identified 2,604 citations with the initial search strategy, including 364 duplicates (fig. 1). Additionally, 3 articles were retrieved from reference lists of selected studies. Of the 2,243 unique articles, 2,190 were discarded after reading the title and abstract. Of the 53 studies selected for full-text review, 3 were not assessed as they were written in Japanese. Of the studies appraised, 19 were excluded because they provided only relative frequencies of the affected genes and syndromes, and not prevalence data; 6 studies reported prevalence rates for single phenotypes or genotypes, 2 studies reported prevalence values from regional studies later included by the same authors in a more wide-ranging study [14, 15], and in 1 study the prevalence rate included patients living outside the reference area [16].

Of the 22 articles selected for this review, 9 included HSP and HCA patients, 9 only HCA and 3 only HSP. No studies were identified reporting prevalence values in a

Table 1. Selected studies and prevalence estimates: HCA

First author	Country (region)	Source of patients ^a	Population	Number	Prevalence per 100,000 people			
					isolated HCA	AD-HCA	AR-HCA	total HCA
Sridharan [26], 1985	Libya (Benghazi province)	multisource	519,000	14	–	–	–	2.7
Brignolio [38], 1986 ^d	Italy (Turin province)	hospitals + families	2,327,996	111	1.1	1.2	2.6	4.8
Polo [4], 1991 ^d	Spain (Cantabria region)	hospitals + families	510,000	54	2.2	1.2	7.2	10.6
Filla [41], 1992 ^d	Italy (Molise region)	multisource	335,211	16		0.0	4.8	4.8
Hirayama [27], 1994	Japan (national)	hospitals	123,000,000	1,431 ^b		1.0 ^b	0.1 ^b	1.1 ^b
Leone [39], 1995 ^d	Italy (Valle d'Aosta region)	multisource	115,270	12	6.9	0.9	2.6	10.5
Jardim [17], 2001 ^d	Brazil (Rio Grande do Sul state)	genetic centres + families	10,000,000	199 ^b	0.1	1.9		
van de Warrenburg [21], 2002 ^d	The Netherlands (national)	genetic centres	15,863,950	391		2.5		
Zhao [37], 2002 ^d	Singapore (national)	genetic centres	3,500,000	58		1.6 ^b		
Zortea [31], 2004 ^d	Italy (Padua province)	hospitals	845,203	79		2.3 ^{b, c}	1.7 ^{b, c}	9.3
Muzaimi [30], 2004	UK (southeast Wales)	multisource	570,000	76	8.4	0.7 ^{b, c}	0.4 ^{b, c}	11.2
Infante [18], 2005 ^d	Spain (Cantabria region)	hospitals + families	527,000	8		1.6		
Tsuji [22], 2008 ^d	Japan (national)	registry	126,900,000 ^b	7,111 ^b		5.0 ^b	0.3 ^b	5.3 ^b
Shibata-Hamaguchi [24], 2009	Japan (Hokuriku district)	hospitals	3,110,000 ^b	132		4.2 ^b	0.0	4.2
Erichsen [20], 2009 ^d	Norway (southeast)	multisource	2,633,893	171		4.2	2.3	6.5
Anheim [52], 2010 ^d	France (Alsace region)	hospitals	1,800,000	95			5.3	
Farghaly [28], 2010	Egypt (Al-Kharga district)	door-to-door survey	62,583	7		–	–	11.2
Joo [29], 2012	Korea (national)	insurance database	48,606,000	2,402		–	–	5.0
Coutinho [23], 2013 ^d	Portugal (national)	multisource	10,322,000	918		5.6	3.3	8.9

Isolated = Isolated patients; Number = number of patients identified in the study; – = the group was included in the study, but the prevalence was not ascertainable from the reported data.

^a Studies were classified according to the main sources of patients, though other complementary sources might have been used. Please refer to online supplementary table 1 for a complete listing of sources used. Multisource studies were defined as studies that in-

clude patients from at least primary care/community settings, specialized/hospital care and active investigation of probands' families.

^b Values not reported by the authors but estimated from the data in the paper.

^c These values are probably underestimated because of a significant number of unclassified patients in this study (>50%).

^d Study included in the meta-analysis.

defined population for forms with X-linked inheritance or mitochondrial inheritance. The number of patients reported ranged from 7 to 7,470 and the reference population from 62,583 to 127,000,000. Overall, the selected studies included 15,820 patients from 16 different countries with a reference population of around 347 million people. The prevalence of AD-HCA ranged from 0.0 to 5.6/10⁵, that of AR-HCA from 0.0 to 7.2/10⁵ (table 1), that of AD-HSP from 0.5 to 5.5/10⁵ and that of AR-HSP from 0.0 to 5.3/10⁵ (table 2). The number of isolated patients with suspected HCA varied from 1.1 to 8.4/10⁵ and that of those with suspected HSP from 0.3 to 1.3/10⁵. The overall prevalence in the studies covering all groups ranged from 1.3 to 20.2/10⁵, and in the multisource population-based studies from 4.8 to 13.9/10⁵.

Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease was the most common form of dominant ataxia in 7 of the 9 studies with genetic testing (online suppl. table 2), reaching the highest relative frequency in Rio Grande do Sul (Brazil) [17], with 89%. SCA2 was the most common form in Cantabria (Spain; 33% of families) [18], and the second most common in Padua (Italy; 45% of patients) [19], southeast Norway [20] and Singapore [17]. SCA6 was the second most common form in the Netherlands [21] and Japan [22]. The number of patients without genetic diagnosis had its lower range at a minimum of 20% of patients (33% of families) in Cantabria [18], while in the study performed in southeast Norway [20], 92% of the families had no genetic diagnosis after thorough testing. In Portugal, 30% of the patients (36% of the families) remained without an identified gene after

Table 2. Selected studies and prevalence estimates: HSP

First author	Country (region)	Source of patients ^a	Population	Number	Prevalence per 100,000 people			
					isolated HSP	AD-HSP	AR-HSP	total HSP
Sridharan [26], 1985	Libya (Benghazi province)	multisource	519,000	11	–	–	–	2.1
Brignolio [38], 1986 ^c	Italy (Turin province)	multisource	2,327,996	31	0.3	0.7	0.3	1.3
Polo [4], 1991	Spain (Cantabria region)	hospitals + families	510,000	49		–	–	9.6
Filla [41], 1992 ^c	Italy (Molise region)	multisource	335,211	9		0.6 ^b	2.1 ^b	2.7
Hirayama [27], 1994	Japan (national)	hospitals	123,000,000	109	–	–	–	0.1
Leone [39], 1995 ^c	Italy (Valle d'Aosta region)	multisource	115,270	5	0.9 ^b	3.4 ^b	0.0	4.3
McMonagle [36], 2002 ^c	Ireland (Northern Ireland and Irish Republic)	hospitals + families	5,436,000	69		1.3		
Tsuji [22], 2008	Japan (national)	registry	126,900,000 ^b	1,103 ^b		–	–	0.9 ^b
Braschinsky [42], 2009 ^c	Estonia (national)	multisource	1,340,000 ^b	59		1.8 ^b	2.6 ^b	4.4
Boukhris [57], 2009 ^c	Tunisia (Sfax district)	hospitals	869,700	50		0.5 ^b	5.3	5.8
Erichsen [20], 2009 ^c	Norway (southeast)	multisource	2,633,893	194	1.3	5.5	0.6	7.4
Coutinho [23], 2013 ^c	Portugal (national)	multisource	10,322,000	418		2.5	1.7	4.1

Isolated = Isolated patients; Number = number of patients identified in the study; – = the group was included in the study, but the prevalence was not ascertainable from the reported data.

^a Studies were classified according to the main sources of patients, though other complementary sources might have been used. Please refer to online supplementary table 1 for a complete listing of

sources used. Multisource studies were defined as studies that include patients from at least primary care/community settings, specialized/hospital care and active investigation of probands' families.

^b Values not reported by the authors but estimated from the data in the paper.

^c Study included in the meta-analysis.

extensive genetic testing [23], and in Japan, 31% of the patients from the Hokuriku district [24] and 37% nationwide [22] had no genetic diagnosis.

Friedreich ataxia was the most frequent form of AR-HCA, with the exception of southeast Norway [20], where ataxia-telangiectasia (A-T) reached a prevalence of 18%. Ataxia with oculomotor apraxia (AOA) was the second most common form in Portugal (12%) [23] and Alsace (France; 10%) [18].

The most common AD-HSP form in every population was spastic paraplegia, autosomal dominant, type 4 (SPG4), with a relative frequency around 40% in most studies (online suppl. table 2). SPG11 was the most frequent AR-HSP, ranging from 15% in Portugal [23] to 21% in the Sfax district (Tunisia) [25]. The number of patients without genetic diagnosis after systematic testing ranged from 45 to 67% in the AD-HSP group, and from 71 to 80% in the AR-HSP group (online suppl. table 2).

Of the 9 studies that reported overall HCA and HSP prevalence values, 2 were excluded from the meta-analysis; in one the number of isolated patients without genetic diagnosis could not be ascertained from the results [26], and the other reported a prevalence from a population with more recent data [27]. In the meta-analysis of

the subgroups, 9 studies were included for AD-HCA, 7 for AR-HCA, 8 for AD-HSP and 6 for AR-HSP. The reasons for exclusion were: subgroup prevalence values not ascertainable from the data [4, 22, 26–29]; >25% of unclassified patients (61% [30] and 57% [31]); data from populations with more recent studies [4, 27]; and regional prevalence study from a country where national prevalence data were available [24].

The meta-analysis estimated an overall prevalence for HCA and HSP of $9.8/10^5$ (95% CI: $6.7\text{--}12.8/10^5$; $I^2 = 98.8\%$). For AD-HCA, the prevalence estimate was $2.7/10^5$ ($1.5\text{--}4.0/10^5$; $I^2 = 99.1\%$), for AR-HCA it was $3.3/10^5$ ($1.7\text{--}4.9/10^5$; $I^2 = 98.7\%$), for AD-HSP $1.8/10^5$ ($1.0\text{--}2.7/10^5$; $I^2 = 95.7\%$) and for AR-HSP $1.8/10^5$ ($1.0\text{--}2.6/10^5$; $I^2 = 94.8\%$). Considering only studies performed after 2000, the overall prevalence was $10.6/10^5$ ($5.22\text{--}15.88/10^5$); for AD-HCA it was $3.2/10^5$ ($1.8\text{--}4.6/10^5$), for AR-HCA $3.2/10^5$ ($1.8\text{--}4.6/10^5$), for AD-HSP $2.2/10^5$ ($1.1\text{--}3.3/10^5$) and for AR-HSP $2.2/10^5$ ($1.2\text{--}3.3/10^5$).

In the regression analysis, no time trend was identified for overall prevalence ($p = 0.45$), for AD-HCA ($p = 0.36$), for AR-HCA ($p = 0.74$) or for AR-HSP ($p = 0.85$). The only significant trend was towards a small but significant increase in the prevalence of AD-HSP over time ($p =$

0.034; $R^2 = 0.56$), estimated at $0.027/10^5$ per year. Concerning the sources used for patient ascertainment, a higher overall HCA and HSP prevalence was reported in studies that performed an active investigation of the probands' families ($p = 0.003$; $R^2 = 0.85$). A significant effect was also reported for AR-HSP ($p = 0.04$; $R^2 = 0.70$), but not for AD-HCA ($p = 0.73$), AR-HCA ($p = 0.63$) or AD-HSP ($p = 0.62$). No significant effect was found when analysing the impact of other sources (hospital records, general practitioner survey, registries and genetic centre records) on overall or subgroup prevalence rates.

Discussion

In this systematic review, we identified 22 studies published since 1983 that reported the prevalence of HCA, HSP or both. Half of the studies [11] were performed in European countries, 5 in Asia, 3 in North African countries and 1 in South America. No studies were found from North America, Sub-Saharan Africa or Oceania. Prevalence studies of HCA and HSP are often performed in regions where clusters of disease have previously been found. Furthermore, surveys that did not find any affected patients may not have been published. Therefore, the prevalence of the reported populations may be higher than non-reported populations. On the other hand, the selected studies (with one exception [28]) are not based on exhaustive screening of a sample or population. Consequently, they represent only minimal prevalence estimates for the areas surveyed. By our search strategy, we identified 3 studies that were not appraised as full texts, as they were written in Japanese and referring to regional Japanese populations [32–34]. Although this could represent a limitation, more recent national data from Japan were available, so that the estimates obtained from these studies would not be included in the meta-analysis. Therefore, their exclusion did not affect the average estimates. The prevalence values show great variation between the studies (tables 1, 2). This was expected, given the distinctive genetic background of the target populations. The frequency in the population of unstable alleles and of haplotypes that are more prone to repeats could explain the variation in ataxias caused by repeat expansions [11]. Diffusion by migration and founder effects in isolated populations could also play a significant role. Furthermore, the prevalence of AR disorders is associated with the frequency of consanguinity in a population [35]. Nevertheless, the differences in prevalence could also be attributable to the heterogeneous methodological ap-

proaches to case finding and to the inclusion, diagnosis and classification of patients. Therefore, some important limitations arise when comparing prevalence estimates across the different studies. They will be discussed in the following paragraphs.

Inclusion and Classification of Patients

The inclusion criteria are not homogeneous. Some studies limit inclusion to late-onset patients [30] or pure phenotypes [4, 36]. The rationale for this restriction is often not stated. Some studies do not clearly define the inclusion criteria used [4, 21, 26, 29, 37] (online suppl. table 1). This issue is especially relevant in studies based on genetic centre records, where clinical inclusion criteria are clearly needed to differentiate clinically affected patients from asymptomatic or presymptomatic carriers. Discrepancies in classification were also found. Many studies do not classify patients based primarily on the mode of inheritance and genetic testing (online suppl. table 1). Some studies report a high number of unclassified patients (61% [30] and 57% [31]), and in two recent publications, the patients were not classified at all [28, 29].

Isolated Patients

The definition of an isolated case differs across studies, as well as the strategy for handling them. Earlier studies reported a high frequency of isolated and/or sporadic cases [4, 38, 39]. At that time, genetic testing was not available, and many HCA and HSP phenotypes had not been clearly described. Anticipation of age at onset in AD-HCA caused by repeat expansions has long been recognized as a cause of isolated cases with progressive ataxia [40]. On the other hand, the underrecognition of cerebellar forms of multiple-system atrophy could also account for the higher share of isolated late-onset cases in earlier studies that did not report cerebellar forms of multiple-system atrophy in their exclusion procedures [18, 38]. In AD-HSP, the late onset and benign nature of some dominant forms could also account for an underrecognition of the disease in previous generations. This was evident in the population-based study from southeast Norway, where 15% of isolated HSP patients obtained a genetic diagnosis [20].

Adjustment of Prevalence Rates

In studies based on surveys of healthcare professionals or institutions, some authors adjusted the prevalence estimates to the response rates [24, 27]. This would imply that non-responding doctors have the same probability of having patients as those doctors who collaborated in the

survey, which is possibly not certain. Most authors who performed this kind of survey did not adjust their results for this parameter [20, 23, 26, 30, 36, 41, 42]. In one study based on patients with an identified gene mutation from genetic centre records [21], the authors adjusted the prevalence estimate to account for patients without the identified gene. Nevertheless, the relative frequency of such patients showed great variation between the studies (online suppl. table 2), so there is some uncertainty in performing this adjustment. Therefore, we present non-adjusted prevalence rates in order to increase comparability between studies.

Average of Pooled Prevalence Rates

All the methodological issues discussed above limit the relevance of pooling prevalence estimates of such a heterogeneous group of studies. However, in order to estimate their worldwide burden, we present the average of the combined HCA and HSP prevalence and the prevalence rate for each subgroup (AD-HCA, AR-HCA, AD-HSP and AR-HSP).

Autosomal Dominant Cerebellar Ataxia

For AD-HCA the prevalence rates found were between 0.0 and $5.6/10^5$, while the pooled average was $2.7/10^5$ (95% CI: $1.5\text{--}4.0/10^5$). The highest prevalence rates were found in the multisource population-based surveys conducted in Portugal [23] and Norway [20], with $5.6/10^5$ and $4.2/10^5$, respectively, and in the registry study in Japan with $5.0/10^5$ [22]. In genetic centre-based studies, prevalence rates were lower, ranging from 1.6 to $2.5/10^5$.

Machado-Joseph disease/SCA3 is present in almost every population described (2 exceptions are Italy [31] and Wales [43]) and is the most frequent form in most of the studies (online suppl. table 2). This has also been implied by genetic centre case series from countries without prevalence studies (USA [44], China [45], France [46], Germany [47] and Taiwan [48]). SCA2 is probably the second most widespread gene worldwide, being the most frequent cause of HCA in Cantabria [18], in Holguín (Cuba) [49] and possibly in some other countries (India [50] and UK [51]). SCA6 and SCA1 are also found in many populations worldwide [18, 20–24, 30, 31, 37]. Dentatorubral-pallidoluysian atrophy is particularly frequent in Asia [20, 22, 37], but also in Portugal [23] and Cantabria [18]. SCA7 and SCA8 are also described in several different countries, while other forms are rare or confined to restricted geographical areas. The number of patients without identified gene after thorough testing for

the most common genes shows great variation between studies, from a minimum of 20% of patients (33% of families) in Cantabria [18] to 92% of families in southeast Norway [20].

Autosomal Recessive Cerebellar Ataxia

In AR-HCA the highest values were reported from Cantabria ($7.2/10^5$) [4] and Alsace ($5.3/10^5$) [52] in two hospital-based studies. The range from multisource studies was 2.3 to $4.8/10^5$. The pooled average was $3.3/10^5$ (95% CI: $1.8\text{--}4.9/10^5$). As the accurate diagnosis of isolated patients with suspect AR-HCA demands thorough clinical, metabolic and genetic studies [53], it is possible that many are not included or stay unclassified in some population-based surveys, due to lack of investigation and follow-up. Perhaps unsurprisingly, a high number of isolated and/or unclassified ataxia patients are associated with lower prevalence values for AR-HCA (table 2). It is likely that, even if early-onset patients are excluded, many of them represent undiagnosed AR-HCA patients.

Friedreich ataxia has long been recognized as the most common cause of AR-HCA worldwide. It has been suggested that A-T is the second most common cause of ataxia [11, 53, 54]. However, in the three studies that tested for both AOA and A-T genes, AOA was found to be more common in two studies (in Portugal and Alsace), while A-T was more common in Norway. The number of patients without molecular diagnosis in the three population-based studies with thorough genetic testing was 37% in Portugal [23], 60% in southeast Norway [20] and 47% in Alsace [52].

Autosomal Dominant Spastic Paraplegia

The range of prevalence rates for AD-HSP was $0.5\text{--}5.5/10^5$, with the highest value reported in southeast Norway [20]. This value is more than double the second highest prevalence reported, $2.5/10^5$ in Portugal [23], although the case finding methods and diagnostic criteria were comparable in both studies. The prevalence in multisource studies ranged from 1.8 to $5.5/10^5$, and in hospital-based studies from 0.5 to $1.3/10^5$. The pooled average was $1.8/10^5$ (95% CI: $1.0\text{--}2.7/10^5$). SPG4 has been found in every population where genetic testing was performed, and has been by far the most frequent cause of HSP. SPG3A is also present in most populations, but with low relative frequency, and SPG31 is even rarer, being identified in two studies. In the two studies that tested families for these three genes, the number of families without molecular diagnosis was 67% [23] and 45% [20].

Autosomal Recessive Spastic Paraplegia

The prevalence of AR-HSP ranged between 0.3 and $5.3/10^5$, these two extremes coming from hospital-based studies. The pooled average was $1.8/10^5$ (95% CI: 1.0– $2.6/10^5$) and the prevalence in multisource studies ranged from 0.6 to $2.6/10^5$. The highest value was found in Tunisia and probably reflects the higher degree of consanguinity found in Northern Africa [25]. The most common form in the three studies that performed genetic testing was SPG11, followed by SPG15 and SPG5. A similar pattern was found in case series from genetic centres [55, 56]. Nevertheless, most families remain without identified genes, ranging from 69% in Tunisia [57] to 82% in Portugal [23].

HCA and HSP with X-Linked and Mitochondrial Inheritance

Although several X-linked and mitochondrial inheritance forms of HCA and HSP have been described, no cases have been reported in the studies reviewed. Nevertheless, some of the studies excluded these forms of inheritance, and most did not systematically perform the required genetic testing. Only one multisource population-based study performed genetic testing for fragile X premutations and POLG mutations; however, none were identified among 171 patients with HCA in south-east Norway [20]. In a cohort of patients previously identified in a prevalence study in southeast Wales [30], only 1 female patient with a fragile X allele in the premutation range was reported among 178 patients with progressive late-onset cerebellar ataxia [43]. Therefore, the suggestion that fragile X premutations could be a frequent cause of late-onset ataxia [58] needs yet to be confirmed in a population-based study. POLG mutations are probably a very rare cause of hereditary ataxia, as has been suggested in non-population-based case series [59–61].

Implications for Future Studies

Studies that used multiple sources generally yielded higher prevalence values than studies based on hospital or genetic centres (tables 1, 2). One important source disregarded in some studies is the investigation of probands' families. The relevance of this source is evident even in population-based studies like the southeast Norway study [20], where 44% of the patients were included after examining family members of probands. In studies reporting the overall HCA and HSP prevalence, the use of this source was significantly associated with higher prevalence. Another crucial point is the assess-

ment of patients for inclusion: a clinical evaluation by experienced neurologists, using defined criteria and supported by genetic testing and family investigation, is recognized by most authors as the standard for diagnosis and inclusion [20, 30, 31, 36, 39, 41, 42, 52] and should be used in future studies. In the genetic testing era, several studies have included some isolated patients as probably hereditary, based on criteria regarding genetic testing, consanguinity, phenotype and auxiliary studies to exclude other entities [20, 23, 31, 42, 52]. In our view, these criteria should be used in future studies; otherwise, the prevalence of recessive forms could be underestimated. This seems to happen in the two studies that report the lowest prevalence values for AR-HCA, also presenting the highest frequency of isolated ataxia [30, 39]. A significant increase in prevalence estimates over time was only identified for the AR-HSP group. Nevertheless, studies published after 2000 showed increased average prevalence rates for every subgroup and for the overall HCA and HSP prevalence, although with confidence intervals overlapping the overall meta-analysis. This increase could be related to the recent contributions by genetic testing to accurate diagnosis. In our view, extensive genetic testing, clinical investigation and follow-up of the patients and their families should be used to reach a precise diagnosis for every patient in future prevalence studies. This would help to exclude alternative diagnoses and enable more homogenous classifications, based primarily on genetic criteria.

Conclusion

The studies on the prevalence of HCA and HSP identified in this review reveal heterogeneous methods and criteria for patient finding, inclusion and classification. The pooled prevalence average yielded a value for HCA and HSP close to 1:10,000 people, whereas the prevalence range in multisource population-based studies is 4.8 – $13.9/10^5$. Most of the identified studies, however, were performed in Europe or Asian countries, and for significant areas of the globe, prevalence rates are as yet unknown. In spite of the advances in molecular research, many patients and families remain without genetic diagnosis, especially in the recessive groups. Therefore, further population-based prevalence studies would be important, not only to estimate the worldwide impact of HCA and HSP but also to provide patient data for molecular research on causes of and future treatments for these diseases.

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