Review

Genetic aspects of Huntington’s disease in Latin America. A systematic review

Castilhos R.M., Augustin M.C., Santos J.A., Perandones C., Saraiva-Pereira M.L., Jardim L.B., on Behalf of Rede Neurogenética. Genetic aspects of Huntington’s disease in Latin America. A systematic review. Clin Genet 2016: 89: 295–303. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2015

We aimed to present a systematic review on Huntington’s disease (HD) in Latin America (LA). PubMed and LILACS were searched up to March 2015, reporting confirmed HD cases in LA. Case series, cross-sectional, case–control, and prospective studies were included. From 534 communications, 47 were eligible. Population-based studies were not found; minimal prevalence of 0.5–4/100,000 was estimated for Venezuela and Mexico. Geographical isolates were well characterized in Venezuela and in Peru. CAG repeats at \( HTT \) gene varied between 7–33 and 37–112 in normal and expanded alleles, respectively. Intermediate alleles were found in 4–10% of controls. Ages at onset and the expanded CAG repeats correlated with \( r \) from –0.55 to –0.91. While haplotype patterns of Venezuelan and Brazilian chromosomes were similar to those observed in Europeans, haplotypes from Peruvian HD patients did not match the same pattern. The limited number of papers found suggests that HD is poorly diagnosed in LA. Minimal prevalence seemed to be halfway between those of Caucasians and Asians. Range of CAG repeats was similar to those of Europeans. Haplotype studies indicate that majority of HD patients might be of Caucasian descent; an Asian origin for some Peruvian patients was proposed.

R.M. Castilhos\(^a,b\), M.C. Augustin\(^c\), J.A. Santos\(^c\), C. Perandones\(^d\), M.L. Saraiva-Pereira\(^e,f,g\), L.B. Jardim\(^a,b,c,f,g,h,i\) and on Behalf of Rede Neurogenética

\(^{a}\)Programa de Pós-Graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, \(^{b}\)Instituto Nacional de Genética Médica Populacional (INAGEMP), Porto Alegre, Brazil, \(^{c}\)Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, \(^{d}\)Parkinson’s Disease and Movement Disorders Program, Hospital de Clínicas, University of Buenos Aires, Buenos Aires, Argentina, \(^{e}\)Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, \(^{f}\)Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, \(^{g}\)Laboratório de Identificação Humana, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, \(^{h}\)Centro de Pesquisa Clínica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, and \(^{i}\)Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Key words: CAG repeats – genetic epidemiology – \( HTT \) gene – Huntington disease – Latin America – polyglutamine diseases

Corresponding author: Laura Bannach Jardim, MD, PhD, Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, 90 035-903, Porto Alegre, Brazil. Tel.: +55 51 3359 8011; fax: +55 51 3359 8010; e-mail: ljardim@hcpa.ufrgs.br

Received 22 April 2015, revised and accepted for publication 7 July 2015
Huntington’s disease (HD) is a progressive autosomal dominant illness characterized by involuntary choreic movements, psychiatry disturbances, and cognitive decline. HD is caused by an expansion of CAG repeats in the coding region of \(HTT\) gene (1). Alleles with up to 35 repeats do not cause disease, but those in the 27–35 range may expand during meiosis and are then called intermediate alleles (IA). Alleles with 36–39 repeats have reduced penetrance (RP); and alleles with more than 40 repeats are always associated with HD in a normal life span. Age of motor onset is inversely correlated with repeat length in the disease-causing range (2).

Western countries with major Caucasian ancestry generally have higher HD prevalence than those found in Asia (3). CAG repeat range found in normal alleles seems to be wider in Caucasians than in Asian population (4), leading to the hypothesis that their pool would be determinant for HD prevalence (5–7). Moreover, intragenic haplogroups more frequently found in European patients seemed to be associated with a higher risk for expansion than other haplogroups (8).

In contrast, data on HD in Latin America (LA) is sparse. In this continent, the peculiar admixture of Amerindian, African, and European ancestries might be associated with different epidemiological characteristics from those found in the original populations, involving CAG repeats range, and clinical and genetic findings of HD patients and families. In order to address this apparent lack of information, our group performed a comprehensive, systematic review on the genetic aspects of HD in Latin American patients, comparing their characteristics with those described in HD patients from other populations.

Materials and methods

Including criteria of studies in this review

All the studies describing HD patients with a molecular diagnosis and with LA ancestry were included. By LA, we mean all Romance-speaking countries of the New World – Mexico in North America; Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama in Central America; Colombia, Venezuela, Ecuador, Peru, Bolivia, Chile, Guyana, Paraguay, Brazil, Argentina, and Uruguay in South America; Cuba, the Dominican Republic, Haiti, and Puerto Rico in the Caribbean.

Case series (with correlation studies), cross-sectional, case–control, and prospective studies, and clinical trials were included. Reviews, comments, editorials, guidelines and experimental studies were not included. Case reports were accepted only when reporting homozygote patients carrying two CAG expanded alleles. Historical articles and portraits were referred in the Historical Background section.

Articles were ordered and organized according to the following queries: HD frequency; distribution of CAG repeats; appearance of new disease-causing alleles; age at onset (AO), correlations with expanded CAG repeats, proportion of juvenile cases and occurrence of HD homozygotes; modifiers of the HD phenotype; fitness and fertility; ancestral haplotypes.

Search methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9). A search in PubMed and LILACS was performed until March 2015 by three investigators (R. M. C., M. C. A., and J. A. S.) independently. List of references were also checked for relevant papers, written in English, Spanish, Portuguese or French, and without restrictions on the following publication status: epub and published manuscripts; abstracts presented in scientific meetings and published thereof. Search terms were (Boolean Operator OR was omitted): (huntington, huntingtina, \(HTT\)) AND (Brazil*, Brasil*, Argentin*, Uruguay*, Paraguay*, Chile*, Bolivia*, Peru*, Ecuador*, Colombia*, Venezuela*, Suriname*, Guyana*, ‘French Guiana’, ‘South America’, ‘Latin America’, ‘Central America’, Caribbean, Panama*, ‘Costa Rica’, Nicaragua*, Honduras*, ‘El Salvador’, Guatemala*, Belize, Mexic*, Cuba*, Haiti*, ‘Dominican Republic’, ‘Puerto Rico’, Jamaica*). We have also searched ClinicalTrials.gov website (http://clinicaltrials.gov/) and the clinical trials section of Orphanet website (http://www.orpha.net) with the term ‘Huntington disease treatment’, in order to find LA researchers participating in ongoing clinical trials. The most recent search was performed in March 2015.

Results

Historical background

First descriptions of HD in LA appeared some years after George Huntington’s paper (10), and were made by Aróstegui in Cuba (1890), by Couto in Brazil (1891), and by Costa in Argentina (1894) (11, 12).

In the second half of the 20th century, LA had a fundamental role in the discovery of the causative gene for HD. The initial descriptions of the geographical isolate of HD families living near Maracaibo lake were done by Americo Negrette (13) and by Ramon Ávila-Girón (14). Following that, regular visits to the Maracaibo Lake were made on behalf of the North American HD research community. Beginning in 1981, a research team from the USA-Venezuela Collaborative Research Project, led by Nancy Wexler, collected hundreds of biological samples, such as blood, sperm, and buccal cells as well as brain specimens after autopsies, from Venezuelan HD patients. This collaborative project led to the identification of HD locus in 1983 and gene identification in 1993 (1, 15–21). Besides the fundamental discovery of the HD gene, the study of families from Maracaibo allowed the understanding of many features of the disease, such as those related to HD homozygotes (22); unstable transmissions of the expanded CAG repeats (23–25); familial and environmental influences on AO (26); mRNA profiles from human HD brains (27); somatic mosaics of...
Genetic aspects of Huntington’s disease in Latin America

Overview of the LA literature on HD

Five hundred and thirty two (30 duplications) articles were initially retrieved from PubMed and LILACS database (Fig. 1). Following abstracts’ revision, 418 references were excluded based on being unrelated to HD, related to animal or cellular HD models, and for being reviews. Further, 19 articles and 12 posters were added by reviewing reference lists of screened articles and consulting HD experts. From the 116 resources selected for full-text analysis, 69 were excluded for not meeting the eligibility criteria.

The majority of studies included were case series of HD patients or families, where correlation studies were performed (Table S1, Supporting Information). In the few case–control studies found, the factor under study was CAG repeats distribution; none has shown sample size estimations. One genome-wide linkage analysis was performed only on HD families (30); because no controls were tested, the study was classified as a case series. Two studies were considered longitudinal: one observation on variation of CAG repeats in sperm samples from the same three HD individuals within a 2 years interval (25), and one report on results of a pre-symptomatic testing program (31).

Frequency of HD in the LA population. Geographical isolates

No population-based studies in LA countries were found. Two papers estimated the minimum prevalence of HD in some LA populations, based on their case series (32, 33) (Table 1). A survey on 691 Mexican patients with molecular diagnosis included cases identified between 1973 and 2008; half of the series originated from Mexico City (32). Another report identified Venezuelan HD patients between 1988 and 2006 from regions other than Maracaibo (33). In both papers, sampling was consecutive and time interval of observations seemed to be of 18 and 37 years respectively, making difficult a meaningful reading.

Other papers reported HD prevalence on geographic isolates (Table 1). The world’s largest concentration of HD patients is in Maracaibo, Venezuela (13, 14, 26, 34). The second isolate was identified in Peru in 1979, in the province of Cañete (12, 35). Reassessment of Peruvian cases shows a spread of Cañete HD descents across the country (36). A third geographical cluster was proposed in Juan de Acosta (37) and in El Dificil, in Colombia (38); a confirmed molecular characterization was obtained (C. Perandones, personal communication). Recent reports suggest the presence of isolates in the Brazilian states of Alagoas (39) and Minas Gerais (40). Characterization of true founder effects in those places is still needed.

Fig. 1. Articles selection flow chart.
CAG repeats distribution in normal and in expanded HTT alleles in LA populations

Five studies evaluated the frequency of normal HTT alleles in controls from LA, with sample sizes varying from 25 to 112 individuals (Table S2). In all but one of these studies, the obtained means or modes varied from 15 to 17.8 repeats (33, 41–43), and were similar to those reported among Caucasians and Asians (4, 5, 8, 44, 45). Normal CAG repeats range in LA overlapped those seen in Caucasians (46) (Table S2).

Twelve LA studies described the distribution of expanded CAG repeats among HD patients (Table S2). Excluding one outermost result likely to be due to ascertainment bias favoring early onset patients (48), the obtained average measurements varied from 41 to 47 CAG repeats (26, 32, 33, 40–43, 49–52).

Three studies have addressed the frequency of IAs in control groups, and other seven studies described IAs found in normal chromosome of their HD case series. Proportion of IAs varied between 2 and 5% of the normal chromosomes analyzed (26, 32, 40–43, 50), with two exceptions, where extremely high proportions of IAs seemed to be due to recruitment of several individuals per family, and to small sample sizes (48, 51).

 Alleles with RP have been found in eight studies (26, 32, 33, 40–43, 49). Table S2 shows the proportion of RP alleles among expanded alleles of each study. Eleven symptomatic individuals carrying RP alleles out of 43 affected HD patients were reported to live in Minas Gerais, Brazil; it was not clear if this clustering occurred in a unique family (40).

New disease-causing alleles

Two studies followed hundreds of transmissions from the Maracaibo cohort (26, 53), and transmissions from 69 IAs were characterized as follows: 65 were stable, 3 alleles contracted, and 1 expanded from 33 to 35 CAG repeats on paternal transmission. Among 44 transmissions from RP alleles, 26 were stable, 1 contracted, and 17 expanded – 6 of them (14%) reached the complete penetrant CAG range.

Two other case series reported five cases in which RP/IA carriers had children with completely penetrant expansions. Three Venezuelan individuals with alleles between 35 and 39 repeats gave birth to four individuals carrying a fully penetrant expanded CAG allele (33). Among Mexicans, two patients with full penetrant alleles were sons of male carriers of IAs of 34 and 35 CAG repeats (32). None of the studies followed the other transmissions, and there is no way to present the data in terms of frequencies or risks.

AO and correlations with the expanded CAG repeats, proportion of juvenile cases, and homozygote cases

Twelve publications reported mean AO, and 10 of them estimated the correlation between AO and expanded CAG repeats distribution in normal and in expanded HTT alleles in LA populations
Genetic aspects of Huntington’s disease in Latin America

Table 2. Latin American studies on age of onset and CAG expanded repeats at HTT gene, and on proportion of juvenile cases. Comparison with Caucasian and Asian samples.

| Population                          | Age at onset, in years, mean (SD) [range] | Correlation between age of onset and the expanded CAG repeat (r)a | Number of cases/families | Juvenile casesb |
|-------------------------------------|-------------------------------------------|------------------------------------------------------------------|--------------------------|-----------------|
| Chile (56)                          | 33.9 (14)                                 | –                                                                | 20/12                    | 15% (3/20)      |
| Brazil (48)                         | 33.9* [12–58]                             | –0.6                                                             | 32/25                    | 12.5% (4/32)     |
| Brazil (42)                         | 41.1± [27–68]                             | −                                                                 | 44/–                     | 5% (2/44)       |
| Venezuela, Maracaibo (26)           | 34.35 [10] [2–84]                         | −0.85                                                            | 443/1?                   | 9% (40/443)     |
| Peru, Cañete (49, 52)               | 40 [12.75] [3–72]                         | −0.718                                                           | 30/17                    | 3.3% (1/30)     |
| Costa Rica (51)                     | 39.3 [10.6] [28–53]                       | −0.78c                                                           | 7/4                      | None            |
| Venezuela, extra-Maracaibo (33)     | Not specified                             | −                                                                | 75                       |                 |
| Mexico (57, 79)                     | 37.4 [12.9] [2–78]                        | −0.72                                                           | 691/401                  | 8% (57/691)     |
| Argentina (41)                      | 35 [14] [4–63]                            | −0.58                                                            | 59/34                    | 17% (10/59)     |
| Brazil (40)                         | 41.7 [10.1] [18–56]                       | −0.84                                                           | 43/21                    | 2.3% (1/43)     |
| Brazil (50)                         | 37.7 [11.8] [6–65]                        | –0.55, one index case per family                                 | 104/93                   | 9.5% (10/104)   |
| Cuba (43)                           | 38 [12.56]                               | −0.82                                                           | 62/16                    | 5% (3/62)       |
| Caucasians                          |                                          |                                                                  |                          |                 |
| Canada (75)                         | 41.5 [12.4] [5–85]                        | −0.69                                                           | 360/259                  | 5.5% (20/360)   |
| Asians                              |                                          |                                                                  |                          |                 |
| China (47)                          | 38 [2–70]                                | −0.62                                                           | 368/–                    | 6.25% (23/368)  |

HD, Huntington’s disease; SD, standard deviation.
aSpearman correlation tests.
bAge at onset ≤ 20 years.
cEstimated from raw data presented in the original papers.

CAG repeat at the HTT gene (Table 2). When stated, AO was defined as the age at the first symptom of disease. The U.S.–Venezuela Collaborative Research Project and Nancy Wexler (2004) (26) noted that AO association with the expanded repeat was stronger in those individuals with expansions longer than 50 repeats. Other reports did not stratify their samples in this way, and showed a single line across the entire range of CAG repeat lengths (32, 40, 41, 43, 48, 50, 52, 54, 55). Figure 2 illustrates some of these findings.

A substantial variation among correlation coefficients between AO and expanded repeats was seen among LA studies (Table 2). This can be a result of differences in sample sizes and/or in ascertainment, although biological reasons cannot be ruled out. For instance, series of 43 (21 families) Brazilian and 62 (16 families) Cuban individuals produced the strongest relationships among LA, with r of −0.84 and −0.82 (40, 43). Clearly, more than two relatives per family were included in both studies. When correlations found in series including relatives are stronger than those found in series with index cases only, a familial effect in cis with CAG expansion is then suggested.

With the exception of an Argentine series recruited in a Pediatric Hospital (41), the proportion of juvenile/infantile cases in most of LA series seems to be similar to those obtained in other populations (26, 32, 40–43, 48, 50, 56) (Table 2).

Confirmed homozygotes were mentioned in two publications (26, 57). Curiously, one of them had similar AO but slower neurological progression when compared to his heterozygous brother (57).

Modifiers of the HD phenotype

Maracaibo isolate is the only LA population where modifier factors were studied to date. A heritability estimate for residual age of onset calculated for 443 individuals has shown that 40% of the residuals were probably determined by other genes while the remaining 60% would be determined by the environmental factors (25, 26). From 12 candidate genes, GRIN2A and TCERG1 were confirmed to be associated to AO (58). A genome-wide linkage analysis (GWAS) was performed in 443 patients with one HTT allele of 40 or more CAG repeats and a known AO and in 360 of their relatives, whose HTT alleles had 35 or fewer CAG repeats. This study suggested that two novel loci on chromosome 2 could modify AO (30).

Genetic fitness and effect of parental age on the offspring

Although large offsprings were associated with HD since the first description by Negrette (34), analytical studies on HD fertility were not found among LA publications.

Sperm analysis of 27 HD individuals found that the range and mean allele size in sperm increased with age (23). In contrast, the CAG repeats length in sperm of two HD individuals was followed during 2 years, and no variation was then shown (25). In 495 transmissions of the HD allele from 206 parents, order of birth was not found to predict repeat-length change in either maternal or paternal transmissions (25).

Possible origins of HD in LA. Haplotype analyses

Haplotype profiles of at least four LA HD case series have been performed, including only CAG CCG repeats...
Castilhos et al.

**Fig. 3.** Haplogroups obtained in Huntington’s disease (HD) and control chromosomes from South Brazil.

(40) or the most usual combination of repeats with VNTRs and single nucleotide polymorphisms (SNPs) (33, 59; James F. Gusella, personal communication).

Using two VNTRs and two SNPs in the promoter region plus CCG repeats in exon 1 and the GAG insertion/deletion in exon 58 (also known as Δ2642), 75 HD individuals were compared to 40 controls (15 related) in Venezuela, extra-Maracaibo (33). Patterns were also compared with data obtained from Colombian, Peruvian, Spanish, Portuguese, and French HD cases. The authors concluded that their patients were probably of European Caucasian origin.

A haplotype study based upon 20 SNPs, CAG repeat, and the indel polymorphism Δ2642 (60), was done in 48 HD index cases and 32 normal, unrelated controls from Rio Grande do Sul State, South Brazil. HTT haplotypes 1 and 2 were the most common (Fig. 3). Haplotype profile on HD chromosomes was very similar to that found in Caucasians from North America and Europe, suggesting that the ancestral origin of most HD chromosomes is a common feature in these populations (Gusella, personal communication).

The HTT haplogroups [based on (8)] of 60 affected Peruvian HD index cases were compared to those of 130 non-affected admixed controls and of 82 Amerindian controls (59). The majority of HD chromosomes in Europe are found in haplogroup A (8), while HD chromosomes in the East-Asian (8) and African (61) populations are mainly associated with haplogroup C. On Peruvian HD chromosomes, haplogroups A and C were found in 85 and 15%, a different haplogroup distribution from those found in European chromosomes (92 and 2%, respectively). Distribution of haplogroups among admixed and Amerindian controls did not show a significant difference from those obtained among Europeans. The authors then raised the hypothesis that Peruvian HD chromosomes carrying haplogroup C might have an Amerindian origin (59).

**Discussion**

This systematic review has shown that knowledge on genetic aspects of HD in LA is weak and sparse, despite the key role played by Latin American HD patients in so many discoveries. The lack of quality and robust articles is a strong argument in favor of systematic reviews, lighting a neglected field of knowledge (62). In a way, this review raised queries beyond the original scope: Latin American health and research systems face considerable problems related to social disparities and budgetary deficiencies (63) that help to explain this lack of knowledge, potentiated by rarity of HD.

The most accepted model for peopling of Americas proposes that Asians ancestors crossed the Bering Strait during the last glaciation, and populated the rest of Americas in a North-South direction (64). Following European arrival in 1492, the composition of LA populations changed dramatically. Interethnic admixture between Amerindians, Europeans, and/or Africans is found everywhere, with large differences according to regions and countries (65). Although one would expect that HD prevalence in LA would be between those found in Caucasians and Asians, ethnic admixture could produce unexpected effects on clinical or genetic characteristics. Evolutionary evidences showed that meiotic instabilities of microsatellites favor the rising of longer alleles (66). Similarly, the huge population expansion that occurred in the last two to three centuries in the New World, varying from few millions of original populations to 600 million inhabitants, was done through a demographic transition characterized by an increased birth rate. Similarly, high birth rates with early onset reproductive periods might have yielded more generations and larger meiotic CAG instabilities than usually expected to a 300–500 years period.

Uptodate, population-based studies on HD frequency are lacking, and even an estimated prevalence of HD in LA remains unclear. Except the documented geographic isolates of Maracaibo and Cañete, which have very high prevalence due to founder effect (26, 12), only two studies estimated minimal prevalence for urban or general populations (32, 33). At first sight, minimal prevalence of HD in Mexico City and in Venezuela fell halfway between those found in Asian and in Caucasian populations (Table 1), which is consistent with the hypothesis formulated above. However, their results should be read critically due to doubts on time frame of both studies.
Genetic aspects of Huntington’s disease in Latin America

HD prevalence has been directly related to normal CAG repeats range in a given population, and this evaluation is crucial to understand HD epidemiology (3, 7, 8). Normal CAG alleles range in LA was more similar to Caucasian than to Asian population (Table S2). However, these estimations were done in small groups from urban centers, and a generalization to the entire LA should be avoided. Populations such as those from the Andes region and others, where estimates of Amerindian ancestry (genetically closer to Asians than to Caucasians) vary from 67 to 98% (65), cannot be represented by those estimates.

Proportion of both IA and RP alleles in the general LA population would be of great interest. IAs were seen in around 6% of Caucasians (46, 67). Inconsistent trends were observed on IA frequencies in general LA populations. Sample sizes studied for IAs in LA – 50 to 188 normal alleles – were too small to assure any proper conclusion.

The range of expanded alleles in LA series or cohorts (26, 32, 33, 40–43, 48–52) seemed to be higher than those obtained elsewhere. Ascertainment biases cannot be ruled out, however: in a frame of wide disparities and fragmentation of health services, the most severe phenotypes might be more easily detected and followed. De novo expansions, resulting from IA instability during meiosis, have been pointed out as the source of uncommon but well-known occurrence of HD patients with no family history. A theoretical estimation proposed that 10% or more of prevalent HD cases would fall in this category (68), and researchers as well as physicians would be interested in confirming this estimation in observational studies in diverse populations. So far, studies followed transmissions among HD families, and not among general population. Sixty-nine IA transmissions in the Maracaibo cohort were strikingly stable (53). This result contrasted with those obtained in a Canadian HD series, where 14% (25 of 181) of the IA transmissions examined gave rise to fully expanded CAG repeats in the offspring (69). Those different results suggest the existence of some in cis factor that could affect expanded CAG repeat, present in one ancestry only. Studies can clarify this matter in the future (70).

The strength of correlations between AO and length of expanded CAG repeat was similar to those found in other populations (Table 2). Bias such as small sample sizes and over-representation of families are noteworthy. Although the last one could be used as a way to suggest family effects on AO, there is no other way to prove it unless testing the effect of the familial relationship on residual AO, a feasible statistical strategy if large sampling is available. In the large Maracaibo series, both predicted and residual AO were estimated, and familial effects other than the expanded CAG repeat accounted for 38% of the residual AO (26).

Studies on modifier genes and on the effect of age of affected parent on the instability of the expanded repeat on LA populations were exclusively performed in the Maracaibo cohort. Although bringing valuable information, data obtained were prone to population stratification, considering that most HD individuals from Maracaibo share a common genetic background.

Ancestral origins of LA HD patients remains a burning issue. Studies performed on populations from Brazil and Venezuela pointed out that LA HD patients shared ancestral haplotypes with Caucasian HD patients. In contrast, Peruvian HD chromosomes present haplogroup C more frequently than European HD chromosomes (59). Authors interpreted this finding as suggestive that some Peruvian HD patients might have a pre-Columbian, Amerindian origin of these mutations. Original haplogroups A, B and C were based upon 21 tag SNPs derived from a European population, where the majority of HD chromosomes were found on haplogroups A (8, 61). HD occurs on haplogroup C at similar absolute frequencies in Europe and East-Asian populations. Lack of other HD haplotypes among Asian HD patients turns haplogroup C the most predominant among these populations (8). Extended haplotypes would be convenient to clarify the origin of haplogroup C in \textit{HTT} chromosomes from Peru.

Conclusions

Although Latin American HD patients were subject of some of the best studies published so far, very little is known on genetic epidemiology of HD in our continent. From a medical and public health perspective, a proper census of the prevalence in the overall population as well as in clusters is of major importance, and no such data is available in LA nowadays. HD is poorly identified and diagnosed in this continent. When diagnosed, information of AO of motor symptoms is largely missing, and this should be pursued in the next reports. Only standard data will contribute with studies on modifier factors. Although a unified haplotype classification is still required for worldwide studies on HD origins, evidence obtained so far suggests that majority of HD patients has a Caucasian inheritance in LA. In general, better studies with cross-sectional and prospective designs are needed in LA. In addition, organization of consortiums as well as multi-centric initiatives might improve the diagnosis and research on HD in LA. Designing better transversal and prospective studies is almost as important as to assure accessibility to established symptomatic treatments and to provide adequate genetic counseling for LA patients and families. All HD patients deserve to receive the same care. Issues such as persistently wide disparities, weak and fragmented health systems, inequitable financing, and sustainability, should be faced (63, 71, 72). Our experience is that research and health systems may grow together. Better-fitted studies on HD prevalence, on CAG repeat distribution and transmission, and on HD phenotype are a huge demand among LA HD patients and families. And finally, research might accelerate accessibility of a growing number of individuals to information, diagnosis, care, and family planning, and might help stimulate the setting up of better health systems throughout the continent, improving autonomy and citizenship among us all.
Conflict of interest

The authors have no conflict of interest to report. The sponsors did not have any role in study design; collection, analysis and interpretation of data; writing of the report and on the decision to submit the report for publication.

Supporting Information

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

Acknowledgements

We would like to thank Dr Ignacio Munoz-Sanjuan for his careful reading and his suggestions to this manuscript. This study was supported by Pesquisa para o Sistema Único de Saúde e Fundo de Apoio à Pesquisa do Rio Grande do Sul. PPSUS FAPERGS, numbers 0700832/2006 and 1209-2551/13-4. R. M. C. received a grant from INAGEMP. J. A. S. and M. C. A. received undergraduate students grants by FAPERGS. M. L. S. P. and L. B. J. were supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico National Counsel of Technological and Scientific Development, Brazil (CNPq).

References

1. The Huntington’s Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington’s disease chromosomes. Cell 1993: 72: 971–983.
2. Losekoot M, van Belzen MJ, Seneca S, Bauer P, Steenhuis AR and Barton DE on behalf of the European Molecular Genetic Quality Network (EMQON). EMQON/CMGS best practice guidelines for the molecular genetic testing of Huntington disease. Eur J Hum Genet 2013: 21: 480–486.
3. Pringsheim T, Wilshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington’s disease: a systematic review and meta-analysis. Mov Disord 2012: 27 (9): 1083–1091.
4. Squitieri F, Andrew SE, Goldberg YP et al. DNA haplotype analysis of Huntington disease reveals clues to the origins and mechanisms of CAG expansion and reasons for geographic variations of prevalence. Hum Mol Genet 1994: 3 (12): 2103–2114.
5. Rubinsztein DC, Amos W, Leggo J et al. Mutational bias provides a model for the evolution of Huntington’s disease and predicts a general increase in disease prevalence. Nat Genet 1994: 7: 525–530.
6. Kremer B, Goldberg P, Andrew SE et al. A worldwide study of the Huntington’s disease mutation. N Engl J Med 1994: 330 (20): 1401–1406.
7. Andrew SE, Hayden MR. Origins and evolution of huntington disease chromosomes. Neurodegeneration 1995: 4: 239–244.
8. Warby SC, Visscher H, Collins JA et al. H7 haplotypes contribute to differences in Huntington disease prevalence between Europe and East Asia. Eur J Hum Genet 2011: 19: 561–566.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009: 6 (7): e1000097.
10. Huntington G. On chorea. Med Surg Rep 1872: 26: 317–321.
11. Huntington G. On chorea. Med Surg Rep 1872: 26: 317–321.
12. Torres-Ramírez L, Esquerre CC, Quispe NM. Actualización sobre la enfermedad de Huntington y experiencia de 30 años en el Instituto Nacional de Ciencias Neurológicas. Diagnostico 2008: 21: 480–486.
13. Pringsheim T, Wilshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington’s disease: a systematic review and meta-analysis. Mov Disord 2012: 27 (9): 1083–1091.
14. Squitieri F, Andrew SE, Goldberg YP et al. DNA haplotype analysis of Huntington disease reveals clues to the origins and mechanisms of CAG expansion and reasons for geographic variations of prevalence. Hum Mol Genet 1994: 3 (12): 2103–2114.
15. Rubinsztein DC, Amos W, Leggo J et al. Mutational bias provides a model for the evolution of Huntington’s disease and predicts a general increase in disease prevalence. Nat Genet 1994: 7: 525–530.
16. Conneally PM, Haines JL, Tanzi RE et al. Huntington disease: no evidence for locus heterogeneity. Genomics 1989: 5 (2): 304–308.
17. Conneally PM, Gilliam TC, Tanzi RE et al. Molecular genetics of Huntington’s disease. Cold Spring Harbor Symp Quant Biol 1986: 51 (P1): 359–364.
18. Conneally PM, Wexler NS, Conneally PM. A molecular genetic approach to Huntington’s disease. Nature 1987: 326 (6109): 194–197.
19. Leeflang EP, Tavare S, Marjoram P et al. Analysis of germline mutation spectra at the Huntington’s disease locus supports a mitotic mutation mechanism. Hum Mol Genet 1999: 8 (2): 173–183.
20. Voon SR, Dubéau L, and Young M, Wexler NS, Arnheim N, Huntington disease expansion mutations in humans can occur before meiosis is completed. Proc Natl Acad Sci USA 2003: 100 (15): 8834–8838.
21. Wheeler VC, Persichetti F, McNeil SM et al. Factors associated with HD CAG repeat instability in Huntington disease. J Med Genet 2007: 44: 695–701.
22. The U.S.-Venezuela Collaborative Research Project and Nancy Wexler. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington’s disease’s age of onset. Proc Natl Acad Sci USA 2004: 101 (10): 3498–3503.
23. Hodges A, Strand AD, Aragaki AK et al. Regional and cellular gene expression. Changes in human Huntington’s disease brain. Hum Mol Genet 2006: 15 (6): 965–977.
24. Shelbourne PF, Keller-McGandy C, Bi WL et al. Triplet repeat mutation length gains correlate with cell-type specific vulnerability in Huntington disease brain. Hum Mol Genet 2007: 16 (10): 1133–1142.
25. Sapp E, Valencia A, Li X et al. Native mutant huntingtin in human brain: evidence for prevalence of full-length monomer. J Biol Chem 2012: 287 (16): 13487–13499.
26. Gayn J, Brocklebank D, Andresen JM et al. Genome-wide linkage scan reveals novel loci modifying age of onset of Huntington’s disease in the Venezuelan HD kindreds. Genet Epidemiol 2008: 32: 445–453.
27. MacDonald ME, Barnes G, Srinu CV, Wexler NS, et al. Gamete but not somatic instability of CAG repeat length in Huntington’s disease. J Med Genet 1999: 30: 982–986.
28. Alonso ME, Ochoa A, Boll MC et al. Clinical and genetic characteristics of Mexican Huntington’s disease patients. Mov Disord 2009: 24 (13): 2012–2015.
29. Paradisi I, Hernández A, Arias S. Huntington disease mutation in Venezuela: age of onset, haplotype analyses and geographic aggregation. J Hum Genet 2008: 53: 127–135.
30. Okun MS, Thommi N. Americo Negrette (1924 to 2003). Diagnosing Huntington disease in Venezuela. Neurology 2004: 63: 340–343.
31. K assigne N. Corea de Huntington: Epidemiologia en el Peru y Terapeutica. Poster presented at the I11 Jornada Cientifica UFCH 1979. December 10 – 15; Lima, Peru.
32. Lovato-Espadin R, Tinamé CR, Alva GT, et al. Huntington’s disease in Peru: Spread of Cases and Analysis of CAG Repeats Distribution. Poster presented at the 60th Annual Meeting of American Society of Human Genetic 2010. November 2–6; Washington DC, USA.
33. Daiza BJ, Caiapha RH, Artetta BJ and et al. Estudio Neuroepidemiologico en Juan de Acosta (Atlantico-Colombia) Julio de 1989 a Julio de 1991. Acta Med Colomb 1992: 17: 324.
34. Martinez V, Ospina-Garcia N, Arroyo-Rauscos M, et al. Descripción de una familia con Enfermedad de Huntington procedente del Distrito de Arquian, Magadalenal. Poster presented at the XI Congresso Colom- biano de Neurolologia 2013. August 15–18; Cartagena, Colombia.
35. Alencar MA. Currently Prevalence of Huntington’s Disease in Feira Grande – Alagoas/Northeastern Brazil. Paper presented at the 2013 World Congress of Huntington Disease. J Huntington Dis 2013: 2 (3): 352.
Genetic aspects of Huntington’s disease in Latin America

40. Agostinho LA, Rocha CF, Medina-Acosta E et al. Haplotype analysis of the CAG and CCG repeats in 21 Brazilian families with Huntington’s disease. J Hum Genet 2012: 57: 796–803.

41. Gatto E, Parisi V, Persi G et al. Clinical and genetic characteristics in patients with Huntington’s disease from Argentina. Parkinsonism Relat Disord 2012: 18: 166–169.

42. Raskin S, Allan N, Teive HAG et al. Huntington disease – DNA analysis in Brazilian population. Arq Neuropsiquiatr 2000: 58 (4): 977–985.

43. Vázquez-Mojeña Y, Laguna-Salvia L, Lafitfa-Mesa JM et al. Genetic features of Huntington disease in Cuban population: Implications for phenotype, epidemiology and predictive testing. J Neurol Sci 2013: 335: 101–104.

44. Carmo-Costa M, Magalhães P, Guimaraes L, Maciel P, Sequeiros J, Sousa A. The CAG repeat at the Huntington disease gene in the Portuguese population: insights into its dynamics and to the origin of the mutation. J Hum Genet 2006: 51: 189–195.

45. Masuda N, Goto J, Murayama N, Watanabe M, Kondo I, Kanazawa I. Analysis of triplet repeats in the huntingtin gene in Japanese families affected with Huntington’s disease. J Med Genet 1995: 32: 701–705.

46. Semaka A, Kay C, Doty CN, Collins JA, Tam N, Hayden MR. High frequency of intermediate alleles on Huntington disease-associated haplotypes in British Columbia’s general population. Am J Med Genet 2013: 162B (8): 864–871.

47. Jiang H, Sun YM, Hao Y et al. Huntington disease: CAG repeat numbers in Chinese patients with Huntington’s disease and controls. Eur J Neurol 2014: 21: 637–642.

48. Lima e Silva TC, Serra HG, Bertuzzo CS, Lopes-Cendes I. Molecular diagnosis of Huntington disease in Brazilian patients. Arq Neuropsiquiatr 2000: 58 (1): 11–17.

49. Cornejo-Olivas MR, Marca M, Ortega O et al. Clinical and molecular characteristics of Huntington’s disease in Peruvian population. Poster presented at the VIII Course of the Latin American School of Human Genetics. 2012 May; Caxias do Sul, Brazil.

50. Castilhos RM, Souza AF, Furtado GV et al. Huntington disease and Huntington disease-like in a case series from Brazil. Clin Genet 2014: 86 (4): 373–377. DOI: 10.1111/cge.12283.

51. Vásquez-Cerdas M, Campos-Ramírez D, Gutiérrez-Doña B, Fernández-Morales H, Morales-Montero F, Cuenca-Berger P. Abordaje del diagnóstico y el manejo de la enfermedad de Huntington y sus familiares. Acta Med Costarr 2011: 53 (3): 136–143.

52. Cornejo-Olivas MR, Inca-Martinez MA, Espinoza-Huertas K et al. Clinical and molecular features of late onset Huntington disease in a Peruvian Cohort. J Huntington’s Dis 2015: 4 (1): 99–105.

53. Brocklebank D, Gayán J, Andresen JM et al. Repeat instability in the 27–39 CAG range of the HD gene in the Venezuelan kindreds: counseling implications. Am J Med Genet Part B 2008: 150B: 425–429.

54. Torres-Ramírez L, Mori-Quispe N, Mendoza-Cabanillas M et al. Estudio clínico molecular de la enfermedad de Huntington en pacientes del Valle de Cañete – Perú. Diagnóstico 2006: 45 (3): 102–108.

55. Vásquez-Cerdas M, Morales-Montero F, Fernández-Morales H, del Valle-Carazo G, Fornaguera-Trías J, Cuenca-Berger P. Diagnóstico molecular de la enfermedad de Huntington en Costa Rica. Acta Med Costarr 2008: 50 (1): 35–41.

56. Cruz-Coke R. Epidemiologia Genetica de Corea de Huntington en Chile. Rev Med Chil 1987: 115: 483–485.

57. Alonso ME, Yescas P, Rasmussen A et al. Homozygosity in Huntington’s disease: new ethical dilemma caused by molecular diagnosis. Clin Genet 2002: 61: 437–442.

58. Andresen JM, Gayán J, Cherny SS et al. Replication of twelve association studies for Huntington’s disease residual age of onset in large Venezuelan kindreds. J Med Genet 2007a: 44: 44–50.

59. Tirado-Hurtado I, Kay C, Cornejo-Olivas M et al. Determination of the origin of Huntington disease based on haplotypes in a Peruvian population – Abstract presented at the 64th Annual Meeting of the American Society of Human Genetics; 2014 October 18–22; San Diego, USA.

60. Lee JM, Gillis T, Mysore JS et al. Common SNP-based haplotype analysis of the 4p16.3 Huntington disease gene region. Am J Hum Genet 2012: 90 (3): 434–444.

61. Baine PK, Kay C, Ketelaar ME et al. Huntington disease in the South African population occurs on diverse and ethnically distinct genetic haplotypes. Eur J Hum Genet 2013: 21: 1120–1127.

62. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001: 323 (7306): 224–228.

63. Horton R, Das P. Universal health coverage: not why, what, or when – but how? Lancet 2015: 385 (9974): 1156–1157.

64. Bonutto SL, Salzano FM. A single and early migration for the peopling of the Americas supported by mitochondrial DNA sequence data. Proc Natl Acad Sci USA 1997: 94 (5): 1866–1871.

65. Salzano FM, Sans M. Interethic admixture and the evolution of Latin American populations. Genet Mol Biol 2014: 37 (Suppl. 1): 151–170.

66. Rubinstein DC, Amos W, Leggo J et al. Microsatellite evolution – evidence for directionality and variation in rate between species. Nat Genet 1995: 10: 337–343.

67. Sequeiros J, Ramos EM, Cerqueira J et al. Large normal and reduced penetrance alleles in Huntington disease: instability in families and frequency at the laboratory, at the clinic and in the population. Clin Genet 2010: 78: 381–387.

68. Falush D, Almqvist EW, Brinkmann RR, Iwasa Y, Hayden MR. Measurement of mutational flow implies both a high new-mutation rate for Huntington disease and substantial underascertainment of late-onset cases. Am J Hum Genet 2000: 68: 373–385.

69. Semaka A, Collins JA, Hayden MR. Unstable familial transmissions of Huntington disease alleles with 27–35 CAG repeats (intermediate alleles). Am J Med Genet Part B 2010: 153B: 314–320.

70. Semaka A, Creighton S, Warby S, Hayden MR. Predictive testing for Huntington disease: interpretation and significance of intermediate alleles. Clin Genet 2006: 70: 283–294.

71. Pineda-Bernal L. Análisis bioético de la investigación de la enfermedad de Huntington en el estado Zulia, Venezuela/A bioethical analysis of Huntington’s disease research in Zulia State, Venezuela. Revista RedBioética/UNESCO. 2010: 1(2): 50–61.

72. Maciel ROH, Cardoso FEC, Chaná-Cuevas P et al. Care of patients with Huntington’s disease in South America: a survey. Arq Neuropsiquiatr 2013: 71 (6): 368–370.

73. Nakashima K, Watanabe Y, Kusumi M et al. Epidemiological and genetic studies of Huntington disease in the San-in area of Japan. Neuroepidemiology 1996: 15: 126–131.

74. Hayden MR, MacGregor JM, Beighton PH. The prevalence of Huntington’s chorea in South Africa. S Afr Med J 1980: 58: 193–196.

75. Fisher SE, Hayden MR. Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. Mov Disord 2013: 29 (1): 105–114.

76. Evans SJW, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington’s disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry 2013 Oct: 84 (10): 1156–1160.

77. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington’s disease in Northern Ireland. J Med Genet 1995: 32: 524–530.

78. Dorsey ER, the Huntington Study Group COHORT Investigators. Characterization of a large group of individuals with Huntington disease and their relatives enrolled in the COHORT study. PLoS One 2012: 7 (2): e29522.

79. Alonso ME, Ochoa A, Sosa AL et al. Presymptomatic diagnosis in Huntington’s disease: the Mexican experience. Genet Test Mol Biomarkers 2009: 13 (6): 717–720.

303