SCA2 predictive testing in Cuba: challenging concepts and protocol evolution

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Abstract Spinocerebellar ataxia type 2 (SCA2) is a neurodegenerative disease caused by a CAG repeat expansion in the *ATXN2* gene. Cuba has the highest prevalence (6.57 cases/10⁵ inhabitants) of SCA2 in the world. The existence of 753 affected individuals and 7173 relatives at risk prompted the development in 2001 of the first predictive testing program in the country. The medical records of over 1193 individuals, who requested the test within a 13-year period, were analyzed retrospectively. The presymptomatic and the prenatal tests had uptake rates of 43.4 and 23.9 %, respectively. Several ethical challenges resulted from this program. These include the

following: (1) withdrawal due to the initial protocol's length; (2) the request to participate by 16 at-risk adolescents; (3) the decision made by ten out of 33 couples with a test-positive fetus to carry the pregnancy to term, leading to de facto predictive testing of minors; (4) the elevated frequency of the *ATXN2* gene large normal alleles (≥ 23 to 31 repeats) in the reference population. These issues have led to major changes in the guidelines of the predictive testing protocol: (1) the protocol length was shortened; (2) the inclusion criteria were expanded to reach at-risk adolescents with an interest in prenatal diagnosis; (3) interdisciplinary follow-up was offered to families in which test-positive fetuses were not aborted; (4) prenatal testing was made available to carriers of large normal alleles with ≥ 27 CAG repeats. The profiles of the participants were similar to those reported for other predictive testing programs for conditions like Huntington disease and familial adenomatous polyposis. The genetic counseling practices at the community level, the ample health education provided to the at-risk population, together with multidisciplinary and specialized attention to the affected families, are lessons from the Cuban experience that can be relevant for other international teams conducting predictive testing for other late-onset neurodegenerative disorders.

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Introduction

On October 28th, 1492, the Italian explorer Christopher Columbus and his crew landed at Cayo Bariay, in the province of Holguín on the northeast of Cuba. For the inhabitants of the archipelago, the Spanish conquest and colonization had

cataclysmic consequences; a combination of cruelty and foreign diseases brought them to the brink of extinction, for which reason they barely contributed to the genetic background of that nation which on the other hand was enriched with the genes of Europeans, Africans, and to a lesser extent Asians and Jews (Barcia et al. 1994).

With a current population of over 11,210,064 inhabitants (Anuario Estadístico de Cuba 2013), Cuba has developed a strong public health system. The National Medical Genetics Network is a good example of that. It consists of 184 clinical geneticists and 837 genetic counselors in the 168 municipalities that make up the country. This means one clinical geneticist for every 92,930 inhabitants and one genetic counselor for every 14,144 inhabitants. Most of the genetic counselors are either family doctors or bachelors in nursing (Lantigua 2013).

Cuba is the country with the world's highest prevalence of spinocerebellar ataxia type 2 (SCA2) (28 cases per 10^5 inhabitants), particularly in the province of Holguín where it reaches around 182 cases per 10^5 inhabitants (Velázquez-Pérez et al. 2009a). This fact supports the hypothesis of a possible founder effect in this region (Auburger et al. 1990; Estrada et al. 1999). The origin of the disease remains a mystery; so far, the accepted hypothesis is that it was brought by the colonizers.

SCA2 is an autosomal dominant late-onset disease caused by the abnormal expansion of CAG trinucleotide repeats in the coding region of the *ATXN2* gene (12q24.1). This leads to the expression of an expanded polyglutamine tract in the ataxin-2 protein. The clinical picture of SCA2 includes a progressive cerebellar syndrome accompanied by saccadic slowing, peripheral neuropathy, autonomic dysfunction, sleep disturbances, cognitive abnormalities, and signs of motor neuron involvement. Nonataxic mutation carriers also present somatic, autonomic, cognitive, and oculomotor disturbances (Velázquez-Pérez et al. 2009a, b, c; Rodríguez-Labrada et al. 2011; Velázquez-Pérez et al. 2014a).

There are 163 affected families in Cuba, encompassing almost 600 SCA2 living patients and approximately 8 000 at-risk individuals; among them, 2060 subjects are SCA2 patients' first-degree relatives (Velázquez-Pérez et al. 2014b). For this reason, in 2000, the National Center for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) was created at Holguín province, to provide these families with specialized health care services.

One year later, a multidisciplinary team designed a protocol for genetic counseling, presymptomatic testing (PST), and prenatal diagnosis (PND) of hereditary ataxias (Paneque et al. 2007), which was written in accordance with the international guidelines for predictive testing in Huntington disease (HD), Machado-Joseph disease, late-onset familial amyloid polyneuropathy with the TTR Met 30 mutation (FAP TTR Met 30), and other late-onset neurodegenerative disorders (European Community Huntington's Disease Collaborative Study Group 1993; Sequeiros 1996).

The CIRAH functions as a tertiary level center; at-risk consultands are usually first counseled by family doctors and genetic counselors at their communities; then, they are referred to their respective municipal or provincial center of genetics, where genetic counseling is also provided, and finally, individuals interested in predictive testing come to the CIRAH to request their inclusion in the program (Cruz-Mariño et al. 2013a; Cruz-Mariño et al. 2013b).

This study reviews the experience of the SCA2 predictive testing program in Cuba along its first 13 years and describes different ethical, psychosocial, and technical challenges that led to major changes in the guidelines of the predictive testing protocol.

Materials and methods

The Cuban program for predictive testing of hereditary ataxias comprises both the presymptomatic testing program and the prenatal diagnosis of SCA2.

The former protocol for the Cuban predictive testing program has been published elsewhere (Paneque et al. 2007). Along these years, the empirical experience together with the revisions of international guidelines (Sequeiros et al. 2010a; Sequeiros et al. 2010b; HDSA 2012; Rodrigues et al. 2012; Skirton et al. 2013; Macleod et al. 2013) led us to make some changes to the program which are under the scope of the present paper.

In general, the Cuban protocol for PST included at least two genetic counseling sessions, a neurological examination and psychological screening/diagnostic evaluations prior to genetic testing. At disclosure, the participants were informed of both alleles' sizes. Psychological follow-up evaluations were offered 1 week, 1 month, 6 months, and 1 year after the genetic testing result disclosure (Cruz-Mariño et al. 2013a).

Access to PND was given to couples with at least one member carrying the *ATXN2* expanded gene (either clinically affected or in a presymptomatic stage). It was required of both members of the couple to be attending in agreement and to have expressed their intention to terminate the pregnancy were the fetus diagnosed as a carrier of the SCA2 mutation. The amniocentesis was performed between the 16th and 20th week of gestation at the Provincial Centre of Genetics of Holguín in all the cases (Cruz-Mariño et al. 2013b).

A retrospective and descriptive study was designed, based on the analysis of the medical records of 1193 individuals who requested their inclusion in the PST and 71 couples that participated in the PND program between February 2001 and September 2014. The sociodemographic data, uptake, and outcome of tests were collected from the genetic database.

All participants were informed about PST and PND procedures and protocol as well as of the possibility of using

information from their clinical records in clinical research and they gave their separate written consent for both. The study was approved by the Institutional Ethics Committee (Cruz-Mariño et al. 2013a; Cruz-Mariño et al. 2013b).

Data analyses were performed using the Statistica software package (StatSoft, Inc., 2003 STATISTICA data analysis software system, version 6. www.statsoft.com).

Results

Program for SCA2 presymptomatic testing

A total of 1193 individuals at 50 % risk for SCA2 requested their inclusion in the PST. Among them, 895 (75 %) completed the protocol. The uptake rate of the SCA2 PST was 43.4 %. Two hundred sixty-four consultands (29.5 %) tested positive while 631 (70.5 %) had negative results (Fig. 1).

There was a predominance of female participants (60 %). The mean age at the time of testing was 37.56 years (range 13–88 years, SD 13.49 years). The main motivations for taking the test were the risk assessment in their descendants, physical and psychological preparation to cope with the disease, and planning for the future.

Withdrawals and SCA2 presymptomatic testing protocol

Two hundred and twenty individuals (18.4 %) withdrew from the PST program (Fig. 1). The vast majority of the

withdrawals (81.4 %) took place during the first 2 years of the program. Another 78 consultands were excluded from the protocol.

One of the reasons for withdrawal, the length of the protocol, was amenable to adjustments. Not only the length but also the order of consultations in the former protocol were modified (Table 1). By placing the neurology consultation before the inscription in the program, the exclusions of individuals due to unmistakable signs of the disease were eliminated. The level of adhesion to the program increased from 72.8 % in 2002 to 92.4 % between 2003 and 2014.

Among the individuals who withdrew, around 10 % spontaneously decided to return to the program some years later, and this time they completed the protocol. They expressed they did not feel prepared to receive the result at the moment when they withdrew, but now, they were ready and concerned about an ongoing pregnancy or the estimation of risk in their descendants.

Access of minors to the predictive testing programs

Sixteen at-risk female teenagers (13 to 17 years) requested their inclusion in the PST program along these years (2001–2014); all of them were pregnant and interested in the risk assessment for their own and their descendants. They expressed their intention to request PND in the case they were carriers, with termination of the gestation if the fetus was a carrier.

Fig. 1 Flowchart illustrating the outcome of the SCA2 predictive testing program in Cuba along 13 years

Table 1 Principal changes in the SCA2 presymptomatic testing protocol

Weeks	Former PST protocol	New PST protocol
1	Inscription	Neurological exam First genetic counseling session Informed consent Inscription Psychological evaluation Psychometric testing First blood sampling
2	Neurological exam First genetic counseling session First blood sampling	Second genetic counseling session Second blood sampling Psychotherapy session
3	—	—
4	Psychological evaluation Psychometric testing Second genetic counseling session Informed consent Second blood sampling	—
5	—	Psychological re-evaluation Results disclosure Psychological support
6	Psychological re-evaluation	Follow up after results disclosure 1 week 1 month 6 months 1 year
7	Results disclosure Psychological support	—
8	Follow-up after results disclosure 1 week 1 month 6 months 1 year	—

The inclusion criteria for the predictive testing protocol were revised and expanded to include at-risk minors either pregnant or planning a pregnancy and with interest in PND of SCA2. A letter signed by the minors and their parents explaining the reasons for the request is the initial step in the approval process.

Program for SCA2 prenatal diagnosis

Regarding the PND, a total of 87 participation requests were received from 71 at-risk couples. Sixty three of these couples (88.7 %) had a member who was identified through the PST program as a presymptomatic carrier, resulting in a PND up-take of 23.9 % among them (Fig. 1).

Thirty-three fetuses were shown to be carriers of the expanded gene. Most of the couples (69.7 %) terminated the

pregnancy while the rest (30.3 %) decided to continue the pregnancy to term. When the test result was noninformative, the majority of the couples (81.8 %) also decided to continue the pregnancy to term.

ATXN2 gene large normal alleles

In the context of the SCA2 PND, 11 fetuses were identified as carriers of large normal alleles (LNA) with genotypes 22/23 (four cases), 22/27 (two cases), 22/30 (three cases), and 22/31 (two cases).

There is an increased risk for meiotic instability of the *ATXN2* gene in alleles with 27–31 CAG repeats. Therefore, prenatal testing was made available for carriers of alleles ≥ 27 CAG repeats which are near the boundary of SCA2 manifestation.

Discussion

SCA2 presymptomatic testing program unique results

Back in 2001, just a few international teams were already able to share their own experiences implementing PST for late onset neurodegenerative diseases. It was a challenge to start the first predictive testing program in our country. Concerns related to the psychological impact and the outcome of such a program led the research team to conduct studies of its acceptability, which showed a high level of acceptance, especially for PND among individuals at risk willing to have healthy children (98.7 %) and to avoid the occurrence of the disease in future generations (Paneque et al. 2001).

An uptake rate comparison between PST for SCA2 and other neurodegenerative conditions like HD reflects a remarkably elevated uptake in the former disease: 43.4 % for SCA2 in Cuba versus 11.5 and 9.2 % for HD in Mexico and Canada, respectively (Alonso et al. 2009; Dufrasne et al. 2011).

The educational campaigns at the beginning of the program, the positive experiences of the participants, and the delivering of counseling to every at-risk individual through genetic counselors working in every municipality of the country have been important factors for attaining such results.

Other international programs for the assessment of hereditary predisposition to cancer exhibit a large uptake as well; it results in around 52 % for hereditary nonpolyposis colon cancer (HNPCC), 45 % for attenuated familial adenomatous polyposis (AFAP), and between 62 and 97 % for familial adenomatous polyposis (FAP) (Douma et al. 2008; Ramsoekh et al. 2007).

For these conditions, preventive options are available that reduce morbidity and mortality. This is not the reality for SCA2, SCA3, HD, or other late onset neurodegenerative conditions so far; probably, the lack of neuroprotective measures prevents many individuals from taking the test.

In the case of FAP TTR Met 30, there are two therapeutical options that significantly alter the psychological burden imposed by this condition: FAP-I patients are offered Tafamidis (Coelho et al. 2013) which may delay the progression of the disease or liver transplantation (Rolim et al. 2006). The patients and their families now see FAP-I as being less threatening than other neurodegenerative diseases such as SCA3 and HD (Rolim et al. 2006; Paneque et al. 2009; Ledo et al. 2013), and this may increase the presymptomatic testing uptake.

The acceptance rates are not only the effect of cultural and personal experiences, but also the result of the intrinsic characteristics of the program itself, which should guarantee a good level of information for the at-risk families. The genetic counseling practice at the community level gives strength and distinction to the Cuban program and provides at-risk individuals with accessible resources to better face their decision-making process (Cruz-Mariño et al. 2013a).

Nevertheless, a common characteristic shared by all these programs is the profile of the consultands. There is a predominance of female participants, the mean age is over 30 years, planning for the future and risk assessment in the descendants are among the main motivations for taking the test and most of the individuals who completed the protocol tested negative (Douma et al. 2008; Alonso et al. 2009; Dufrasne et al. 2011; Rodrigues et al. 2012).

Redesigning the presymptomatic testing protocol

The highest level of withdrawals from the SCA2 PST program took place during the first 2 years (2001–2002). By this period, there were not many reports in the literature that would allow the comparison of results with other research groups. Therefore, efforts were made to try and understand why some consultands were leaving or resulted excluded from the protocol after their inscription and mainly following the second appointment.

Three main causes for withdrawal were identified: the fear to be unable to cope with an unfavorable result, the better understanding of test implications after genetic counseling, and the protocol's length. Most of the exclusions were due to the presence of clinical features of the disease in these consultands (Cruz-Mariño et al. 2013a).

Once the test for SCA2 PST was available, the enthusiasm for taking it was high among the at-risk families; nevertheless, the level of knowledge related with the test implications was still inadequate. Some of the individuals who requested their inscription in the program realized they were not ready to receive the information or to cope with a positive result after receiving the first genetic counseling session. The fact that many of them have rejoined the program some years later is an expression of the legitimacy of their decision to withdraw at first.

Originally, multistep predictive testing protocols were developed aiming at protecting individuals from the potential psychological damage and to ensure that individuals undergoing testing could make a thoroughly considered decision (Hawkins et al. 2011). These were concepts taken into account in the development of the SCA2 PST former protocol, which included five in-person appointments until receiving the test results (6 weeks after the inscription) as well as the follow-up consultations (Paneque et al. 2007).

However, the protocol's length was pointed out as the third most common cause for withdrawal in the Cuban program (Cruz-Mariño et al. 2013a). Consequently, it was shortened and reorganized while continuing to perform all the evaluations previously undertaken (Table 1). In the new protocol, the test results are given during the third in-person appointment, only 4 weeks after being enrolled in the program. Psychological follow-up is then offered 1 week, 1 month, 6 months, and 1 year after the result communication session (similarly to the previous protocol).

It has been suggested that the length of testing protocols could be viewed as paternalistic, overly time-consuming, and infringing upon a person's "right to know" (Dufrasne et al. 2011). Some authors consider that multiple in-person appointments may contravene the principle of justice and fair resource allocation (Hawkins and Hayden 2011). Additionally, it has been more and more accepted that the adjustment of the protocol extension on a "case by case" basis attending to the discussion of the needs and expectations of every consultand are relevant aspects for an effective counseling practice in the context of PST for late onset neurodegenerative diseases (Guimarães et al. 2013; Skirton et al. 2013; Paneque et al. 2014).

Regarding the reorganization of the consults, in the former protocol, the individuals would be enrolled in the program immediately after their request during the first appointment and the neurological exam would take place in the second appointment. When unmistakable features of the disease were identified during the neurological consultation, these individuals would be excluded from the program.

At present, the neurological evaluation, first genetic counseling session, and psychological assessment precede the enrolment—this avoids exclusion later in the process. There are nonetheless some individuals in denial about their symptomatic stage who request to participate in the PST protocol; these cases benefit at large from the psychological support offered along the program, this is why they are inscribed despite their clinical manifestations.

Current recommendations for predictive testing in HD do not consider the neurological exam as a requirement for participation, but rather as an important baseline evaluation of each person (MacLeod et al. 2013).

We believe that the level of adherence to the Cuban program between 2003 and 2014 is related to the protocol's gradual evolution in response to the needs of the participants, together with the positive impact of the program in the population.

The dilemma of predictive testing in minors

There are no medical benefits in testing minors for late-onset neurodegenerative diseases when preventive measures or interventions are not available. SCA2 predictive testing in minors has no advantages and should not be undertaken (Sequeiros et al. 2010b). Similarly, in HD, the age of majority is recommended as the minimum age for testing (MacLeod et al. 2013). A very different scenario accounts for those children at risk for FAP who need regular surveillance when carrying the mutated gene. They will virtually all develop colorectal cancer and will need annual endoscopic screening and colectomy when the polyps appear (Codori et al. 2003).

The fact that 16 at-risk Cuban teenagers were already pregnant and requesting PND as a reproductive option made it

necessary to review and to expand the inclusion criteria. Because they were capable of choosing testing, request the test by themselves, and appeared to understand the implications of the potential result, the genetic testing would provide them with the psychological benefit of relieving anxiety (Cruz-Mariño et al. 2013c).

Besides the risks of pregnancy in adolescence, the disadvantages of the almost simultaneous inclusion in PST and PND are main concerns underlying the self-referral of these teenagers. The management of every case as well as the outcome of these tests and pregnancies has been published elsewhere (Cruz-Mariño et al. 2013c).

For such cases, additional consultations are performed in order to assess the degree of maturity, voluntariness, and adequate understanding of the information. The psychological attention is reinforced, and the personal pathological antecedents, ego strengths, coping strategies, social support available, and familial issues are widely discussed.

Pregnancies with test-positive fetuses carried to term

One third of the couples with test positive fetuses decided to continue the pregnancy to term resulting in a predictive test for their unborn children. Despite the fact that a similar situation has occurred in PND programs for HD in other countries (Simpson et al. 2001; Simpson et al. 2002; Creighton et al. 2003), it has been a motive of great concern for us.

During the genetic counseling sessions and the psychological evaluations of the at-risk couples, the feelings and opinions toward pregnancy termination are explored as deeply as possible. Only those couples completely sure about their intention to terminate the pregnancy if the fetus tests positive are included in the program.

Several reasons have influenced the change of decision regarding pregnancy termination in these couples, among them: the simultaneous request for predictive and prenatal testing, the result of a fetus carrier of the mutation in a previous pregnancy, the absence of children at the time of the study, and the advanced gestational age by the time when the results are disclosed. Similarly, the strong motivation of having children contributed to the continuation of pregnancy in the cases where a noninformative result was obtained (Cruz-Mariño et al. 2013b).

Making the decision of terminating or continuing the pregnancy is always challenging for the at-risk couples, and termination is associated with considerable trauma (Simpson et al. 2002). There were some similarities among those couples who decided to continue the pregnancy to term: the gender of the carrier progenitor was female, all were married or in a common-law relationship and their educational level was secondary school or higher (Cruz-Mariño et al. 2013b).

Since we are aware of the ethical, legal, and psychosocial implications of the predictive testing in unborn

children which resulted from the nontermination of an affected pregnancy (Simpson et al. 2002; Creighton et al. 2003), we have offered to these families an interdisciplinary follow-up, but except for one of them, the rest have declined this service until now. This is another example of the decision-making process complexity when dealing with predictive studies for late-onset diseases.

Expanding the risk boundaries in SCA2 prenatal diagnosis

Traditionally, for having access to the SCA2 PND program, at least one member of the couple should carry the *ATXN2* expanded gene (Paneque et al. 2007). With the inclusion of more couples in the PND, we began to observe in the fetuses and their parents an unexpected increased frequency of LNAs, coming either from the carrier progenitor or from the healthy one alike.

The meiotic instability of CAG repeats in the *ATXN2* expanded gene has a trend toward expansions in 80 % of the transmissions in the Cuban population (Velázquez-Pérez et al. 2009a), but the behavior of LNAs is not yet completely understood.

A research project developed at CIRAHA demonstrated that the Cuban population has a continuous distribution of LNAs from 25 to 30 CAG repeats as well as an elevated frequency of large normal and intermediate alleles. Similarly to expanded alleles, LNAs of 27–31 CAG repeats are somatically unstable; they have a different molecular nature and behavior resembling the intermediate alleles (32–34 CAG) (Laffita-Mesa et al. 2012; Laffita-Mesa et al. 2014).

These LNAs could represent a source for the generation of new expanded alleles in the general population through meiotic instability. In the context of the Cuban PND program, we have observed either marked stability in some families versus expansions in others (Cruz-Mariño et al. 2014), thus supporting the notion that carrying a LNA is not sufficient for the generation and transmission of an expanded allele, probably a particular haplotype underlies their meiotic instability.

The evidence points to the allele with 27 CAG repeats as the threshold for a higher instability risk (Laffita-Mesa et al. 2012). This is why SCA2 PND is now available not only for carriers of expanded alleles but also for those persons carrying LNAs ≥ 27 CAG repeats who must be aware of the risk for their descendants if a CAG expansion takes place in the *ATXN2* gene during meiotic events.

The identification of SCA2 LNAs as a risk factor for amyotrophic lateral sclerosis (ALS) and the possible genetic link between ALS and SCA2 (Elden et al. 2010; Daoud et al. 2011; Laffita-Mesa et al. 2013) pose a new challenge for this program. Even among those families where some members

carrying SCA2 LNAs have been affected with ALS, the accurate prediction of the phenotype for other LNAs carriers is not possible at present.

The high frequency of such alleles not only in SCA2 families but also among individuals from the Cuban general population together with the current knowledge limitations indicate the direction that research must be focused on in the years to come.

SCA2 presymptomatic gene carrier: a closer look to the concept

Since the first description of the hereditary ataxias, their onset has been related to the appearance of their main symptom: the ataxia. Nevertheless, the neurodegenerative process starts many years before. The identification of other prodromal signs has widened our understanding of the natural course of these conditions.

In SCA2, these early manifestations can be detected even 15 years before the onset of ataxia, including cramps, sensory symptoms, hyperreflexia, sleep and autonomic disorders, as well as olfactory and cognitive dysfunctions. Besides, there are alterations in the sensory and motor central pathways at intraxial levels and reduced saccade velocity. Imaging studies reveal an early atrophy of the cerebellum and brainstem (Velázquez-Pérez et al. 2009a, b, c; Rodríguez-Labrada et al. 2011; Velázquez-Pérez et al. 2014a).

These findings are not pathognomonic for SCA2, but in the context of individuals at risk who have been identified as gene carriers through the PST, they subtly herald the beginning of the so-called “symptomatic period.”

The comprehensive characterization of this “nonataxic” stage of the disease also poses a challenge for the genetic counseling to be provided to at-risk individuals. Should the “presymptomatic” concept be revisited, the onset of the disease could be placed up to 15 years before the onset of ataxia.

The implications of this knowledge go far beyond the redefinition of the disease onset; a better understanding of the timing and pathways responsible for neurodegeneration will allow a more accurate estimation of the time left free of ataxia, a common concern in presymptomatic consultands. At the same time, it provides a unique opportunity for the design and implementation of therapies in very early stages of the disease when they should be most effective.

Conclusions

Either as heritage from the conquerors giving place to a founder effect or as the result of a pool of LNAs prone to instability, the SCA2 became a serious health problem for the Cuban population. Pioneering the program for its predictive testing has been a challenging experience.

Over 13 years, the multidisciplinary team at CIRAHA has followed every consultand with a personalized approach, incorporating their individual needs to the gradual modification of the testing protocol, this leading to major changes in the guidelines: (1) the protocol length was shortened; (2) the inclusion criteria were expanded to reach at-risk adolescents with interest in prenatal diagnosis of SCA2; (3) interdisciplinary follow-up was offered to families in which test-positive fetuses were not aborted; (4) prenatal testing was made available to carriers of large alleles within the reference range, particularly those with ≥ 27 CAG repeats.

The genetic counseling practices at the community level, the ample health-education provided to the at-risk population, together with a multidisciplinary and specialized attention to the affected families, are lessons from the Cuban experience that can be relevant for other international teams conducting predictive testing for other late-onset neurodegenerative disorders.

Further research is needed to continue improving the predictive testing practice as well as to identify community and sociocultural characteristics that play a role while offering genetic counseling in different populations.

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Compliance with ethical guidelines The presymptomatic testing and the prenatal diagnosis procedures are in compliance with the laws existing in Cuba. They are in accordance with the ethical standards of CIRAHA and with the Helsinki declaration of 1975 as revised in 2000. All participants were informed about PST and PND procedures and protocol, as well as the possibility of using information from their clinical records in clinical research and they gave their separate written consent for both.

Conflict of interest Authors declare no conflicts of interest

References

- Alonso ME, Ochoa A, Sosa AL et al (2009) Presymptomatic diagnosis in Huntington's disease: the Mexican experience. *Genet Test Mol Biomark* 13(6):717–720
- Anuario Estadístico de Cuba (2013) <http://www.one.cu/aec2013/datos/03%20Poblacion.pdf>. Accessed 29 Dec 2014
- Auburger G, Orozco G, Ferreira R et al (1990) Autosomal dominant ataxia: genetic evidence for locus heterogeneity from a Cuban founder effect population. *Am J Hum Genet* 46(6):1163–1177
- Barcia MC, García G, Torres-Cuevas E (1994) Historia de Cuba. La Colonia. Evolución socioeconómica y formación nacional. Tomo 1. Editora Política. La Habana, p 518. ISBN 9590100368, 9789590100369
- Codori AM, Zawacki KL, Petersen GM et al (2003) Genetic testing for hereditary colorectal cancer in children: long-term psychological effects. *Am J Med Genet A* 116A(2):117–128
- Coelho T, Maia LF, da Silva AM et al (2013) Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. *J Neurol* 260(11):2802–2814
- Creighton S, Almqvist EW, MacGregor D et al (2003) Predictive, prenatal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987 to 2000. *Clin Genet* 63(6):462–475
- Cruz-Mariño T, Velázquez-Pérez L, González-Zaldívar Y et al (2013a) The Cuban program for predictive testing of SCA2: 11 years and 768 individuals to learn from. *Clin Genet* 83(6):518–524
- Cruz-Mariño T, Velázquez-Pérez L, González-Zaldívar Y et al (2013b) Couples at risk for spinocerebellar ataxia type 2: the Cuban prenatal diagnosis experience. *J Community Genet* 4(4):451–460
- Cruz-Mariño T, Velázquez-Pérez L, González-Zaldívar Y et al (2013c) Cuban Adolescents Requesting Presymptomatic Testing for Spinocerebellar Ataxia Type 2. *ISRN Genetics*, vol. 2013, p 5. doi:10.5402/2013/837202
- Cruz-Mariño T, Laffita-Mesa JM, González-Zaldívar Y et al (2014) Large normal and intermediate alleles in the context of SCA2 prenatal diagnosis. *J Genet Couns* 23(1):89–96
- Daoud H, Belzil V, Martins S et al (2011) Association of long ATXN2 CAG repeat sizes with increased risk of amyotrophic lateral sclerosis. *Arch Neurol* 68(6):739–742
- Douma KFL, Aaronson NK, Vasen HFA, Bleiker EMA (2008) Psychosocial issues in genetic testing for familial adenomatous polyposis: a review of the literature. *Psychooncology* 17(8):737–745
- Dufresne S, Roy M, Galvez M, Rosenblatt DS (2011) Experience over fifteen years with a protocol for predictive testing for Huntington disease. *Mol Genet Metab* 102(4):494–504
- Elden AC, Kim HJ, Hart MP et al (2010) Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* 466(7310):1069–1075
- Estrada R, Galarraga J, Orozco G et al (1999) Spinocerebellar ataxia 2 (SCA2): morphometric analyses in 11 autopsies. *Acta Neuropathol* 97(3):306–310
- European Community Huntington's Disease Collaborative Study Group (1993) Ethical and social issues in presymptomatic testing for Huntington's disease: a European Community collaborative study. *J Med Genet* 30(12):1028–1035
- Guimarães L, Sequeiros J, Skirton H, Paneque M (2013) What counts as effective genetic counselling for presymptomatic testing in late-onset disorders? A study of the consultand's perspective. *J Genet Couns* 22(4):437–447
- Hawkins AK, Hayden MR (2011) A grand challenge: providing benefits of clinical genetics to those in need. *Genet Med* 13(3):197–200
- Hawkins AK, Ho A, Hayden MR (2011) Lessons from predictive testing for Huntington disease: 25 years on. *J Med Genet* 48(10):649–650
- HDSA (2012) Genetic testing for Huntington's disease: its relevance and implications. US Huntington's Disease Genetic Testing Group Revised 2003. Retrieved November 26, 2012, from <https://www.hdsa.org/living-with-huntingtons/publications/index.html>
- Laffita-Mesa JM, Velázquez-Pérez L, Santos-Falcón N et al (2012) Unexpanded and intermediate CAG polymorphisms at the SCA2 locus (ATXN2) in the Cuban population: evidence about the origin of expanded SCA2 alleles. *Eur J Hum Genet* 20(1):41–49
- Laffita-Mesa JM, Rodríguez-Pupo JM, Moreno-Sera R et al (2013) De novo mutations in ataxin-2 gene and ALS risk. *PLoS One* 8(8), e70560. doi:10.1371/journal.pone.0070560
- Laffita-Mesa JM, Almaguer-Mederos LE, Kouri V et al (2014) Large normal alleles and SCA2 prevalence: lessons from a nationwide study and analysis of the literature. *Clin Genet* 86(1):96–98
- Lantigua AC (2013) An overview of genetic counseling in Cuba. *J Genet Couns* 22(6):849–853

- Ledo S, Paneque M, Rocha JC et al (2013) Predictive testing for two neurodegenerative disorders (FAP and HD): a psychological point of view. *Open J Genetics* 3:270–279
- MacLeod R, Tibben A, Frontali M et al (2013) Recommendations for the predictive genetic test in Huntington's disease. *Clin Genet* 83(3): 221–231
- Paneque M, Santos-Falcón N, Tamayo CV et al (2001) Type 2 spinocerebellar ataxia: acceptance of prenatal diagnosis in descendants at risk. *Rev Neurol* 33(10):904–908
- Paneque HM, Prieto AL, Reynaldo RR et al (2007) Psychological aspects of presymptomatic diagnosis of spinocerebellar ataxia type 2 in Cuba. *Community Genet* 10(3):132–139
- Paneque HM, Lemos C, Sousa A et al (2009) Role of the disease in the psychological impact of pre-symptomatic testing for SCA2 and FAP ATTRV30M: experience with the disease, kinship and gender of the transmitting parent. *J Genet Couns* 18(5):483–493
- Paneque M, Mendes A, Guimarães et al (2014) Genetics Health Professionals' Views on Quality of Genetic Counseling Service Provision for Presymptomatic Testing in Late-Onset Neurological Diseases in Portugal: Core Components, Specific Challenges and the Need for Assessment Tools. *J Genet Couns*. doi:10.1007/s10897-014-9784-6
- Ramsoekh D, van Leerdam ME, Tops CMJ et al (2007) The use of genetic testing in hereditary colorectal cancer syndromes: genetic testing in HNPCC, (A)FAP and MAP. *Clin Genet* 72(6):562–567
- Rodrigues CSM, Oliveira VZ, Camargo G et al (2012) Presymptomatic testing for neurogenetic diseases in Brazil: assessing who seeks and who follows through with testing. *J Genet Couns* 21(1):101–112
- Rodríguez-Labrada R, Velázquez-Pérez L, Canales-Ochoa N et al (2011) Subtle rapid eye movement sleep abnormalities in presymptomatic spinocerebellar ataxia type 2 gene carriers. *Mov Disord* 26(2):347–350
- Rolim L, Leite A, Ledo S et al (2006) Psychological aspects of presymptomatic testing for Machado-Joseph disease and familial amyloid polyneuropathy type I. *Clin Genet* 69(4):297–305
- Sequeiros J (1996) Protocolo geral do Programa Nacional de Teste Preditivo e Aconselha-mento Genético na Doença de Machado-Joseph. In: Sequeiros J (ed) *O Teste Preditivo da Doença de Machado-Joseph*. Porto, UniGENe, pp 123–149
- Sequeiros J, Martindale J, Seneca S (2010a) Consensus and controversies in best practices for molecular genetic testing of spinocerebellar ataxias. *Eur J Hum Genet* 18(11):1188–1195
- Sequeiros J, Martindale J, Seneca S (2010b) EMQN best practice guidelines for molecular genetic testing of SCAs. *Eur J Hum Genet* 18(11):1173–1176
- Simpson SA, Harper PS, On behalf of the UK Huntington's Disease Prediction Consortium (2001) Prenatal testing for Huntington's disease: experience within the UK 1994-1998. *J Med Genet* 38(5):333–335
- Simpson SA, Zoetewij MW, Nys K et al (2002) Prenatal testing for Huntington's disease: a European collaborative study. *Eur J Hum Genet* 10(11):689–693
- Skirton H, Goldsmith L, Jackson L, Tibben A (2013) Quality in genetic counselling for presymptomatic testing—clinical guidelines for practice across the range of genetic conditions. *Eur J Hum Genet* 21(3): 256–260
- Velázquez-Pérez L, Cruz-Sánchez G, Santos-Falcón N et al (2009a) Molecular epidemiology of spinocerebellar ataxias in Cuba: insights into SCA2 founder effect in Holguin. *Neurosci Lett* 454(2):157–160
- Velázquez-Pérez L, Díaz R, Pérez-González R et al (2009b) Motor decline in presymptomatic spinocerebellar ataxia type 2 gene carriers. *PLoS One* 4(4):e5398
- Velázquez-Pérez L, Seifried C, Abele M et al (2009c) Saccade velocity is reduced in presymptomatic spinocerebellar ataxia type 2. *Clin Neurophysiol* 120(3):632–635
- Velázquez-Pérez L, Rodríguez-Labrada R, Canales-Ochoa N et al (2014a) Progression of early features of spinocerebellar ataxia type 2 in individuals at risk: a longitudinal study. *Lancet Neurol* 13(5): 482–489
- Velázquez-Pérez L, Rodríguez-Labrada R, Cruz-Rivas EM et al (2014b) Comprehensive study of early features in spinocerebellar ataxia 2: delineating the prodromal stage of the disease. *Cerebellum* 13(5): 568–579