The Cuban program for predictive testing of SCA2: 11 years and 768 individuals to learn from

Having reported the world’s highest prevalence of spinocerebellar ataxia type 2 (SCA2), health professionals in Cuba developed a program for the predictive testing of this condition. Between February 2001 and December 2011, a total of 1050 individuals requested their inclusion in the presymptomatic testing (PST) program. Their medical records were retrospectively analyzed in the present descriptive study. A total of 768 participants completed the protocol, 204 withdrew and 78 were excluded. The PST uptake was 24.91%. Females predominated and 70.96% had negative test results. Their main motivations were risk assessment in their descendants, physical and psychological preparation to cope with the disease and planning for the future. The profile of Cuban participants in the predictive testing program is similar to the one reported for other programs all over the world, nevertheless the genetic counseling practice at the community level is a distinctive aspect, which is valuable in providing at-risk individuals with wide and proper knowledge before their testing inclusion request. The SCA2 predictive testing program has high uptake rates and is renowned in our population. Future research is needed to assess the long-term psychological impact in the participants, their partners and relatives.

Conflict of interest

Authors declare no conflicts of interest.
Advances in molecular genetics led to a new era in the field of diagnosis, with the implementation of presymptomatic testing (PST), prenatal diagnosis (PND), and pre-implantation genetic diagnosis for many hereditary neurodegenerative conditions (1–4).

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disease, mainly characterized by a progressive cerebellar syndrome (ataxic gait, cerebellar dysarthria, dysmetria, and dysdiadochokinesia) associated with saccadic slowing, peripheral neuropathy, cognitive disorders and late onset (5).

Around 15 years before the onset of ataxia, slowing of horizontal saccades at 60° of target displacement is present as the earliest subclinical sign in presymptomatic subjects, followed by the reduction of rapid eye movement (REM) sleep percentage with decreased REMs’ density (6).

Having reported the world’s highest prevalence of SCA2 (6.57 cases/10<sup>5</sup> inhabitants) and the greatest number of at-risk descendants (7173) (5, 7), as soon as the mutated gene was identified (8–10) a protocol for genetic counseling, PST and PND of the condition was developed by health professionals in Cuba, guided by the international guidelines for predictive testing in Huntington’s disease (HD), Machado–Joseph disease (MJD) and other hereditary ataxias (1, 2).

After being approved by the Ethics Committees of the Medical College of Holguín and the Centre for Research and Rehabilitation of Hereditary Ataxias (CIRAH), the PST program was started on February 2001. Access was given to non-symptomatic individuals at 50% risk, over 18 years, who had no severe psychiatric disturbances. The SCA2 mutation should have been identified in a relative (11, 12).

During the first 2 years of the program people were informed through educational campaigns, simultaneously, multidisciplinary teams belonging to the local health areas actively offered PST at the communities. Subsequently, a National Network of Medical Genetics that serves the entire country was created; it includes more than 100 clinical geneticists and at least two genetic counselors per municipality (medical doctors, nurses or psychologists with a master degree) (13). Thus, first participants’ experiences and genetic counseling actions became the main source of knowledge regarding the program for at-risk families.

Preliminary impact studies showed the absence of catastrophic events and a positive balance on psychosocial impact, evidenced through the first participants’ high levels of satisfaction (11, 12, 14). Clinical experience, international reports on PST, and revisions of international guidelines (15–17) led us to slightly adapt the program.

This paper reviews the 11-year experience with predictive testing for SCA2 respecting the pre-test opinions about different aspects of the PST and the profile of at-risk individuals who have undergone the test along this period.

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Materials and methods

A retrospective and descriptive study was designed, based on the analysis of the medical records belonging to 1050 individuals who requested their inclusion in the PST program between February 2001 and December 2011. The medical records of 768 at-risk individuals who went through all the protocol were selected, in order to describe these individuals profile as well as their pre-test opinions about different aspects of the PST.

The predictive protocol used during the period of study included at least two genetic counseling sessions, a neurological examination and psychological screening/diagnostic evaluations prior to genetic testing (in order to estimate whether consultands were able to handle results). At disclosure, the participants were informed of both alleles sizes, this information being also relevant for other family members (18).

Psychological follow-up evaluations were offered 1 week, 4 week, 6 month and 1 year after genetic testing results disclosure (11).

In addition to the psychological test batteries, an anamnisis guide was used to obtain socio-demographic data, psychological antecedents and personal history. During the interview performed at the enrolment in the program, we addressed motivations for taking the test, and explored the anticipated changes in response to the results of the test; we also asked to whom they would disclose the test results.

All participants were informed about PST 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. The study was approved by the Institutional Ethics Committee. Throughout the program all the medical records were centrally archived in the Predictive Genetics Department at CIRAH and individually searched for the purpose of this study.

Data analyses were performed using the software STATISTICA 6.1 (USA, 2003) and included descriptive statistics and proportion comparisons through $\chi^2$ test. Significance was defined for $p < 0.05$.

Results

Presymptomatic testing

Seven hundred sixty-eight (73.14%) of 1050 individuals at 50% risk for hereditary ataxias (Fig. 1) completed the protocol, while 204 withdrew (19.43%) and 78 were excluded (7.43%). Taking into account the 3083 asymptomatic at-risk individuals reported for this population who are first-degree relatives of affected subjects (3), we estimate that the program has an uptake of around 24.91%.

Those who withdrew did so at different stages of the testing protocol: 76.96% of them after the first genetic counseling session and 23.04% after the second counseling session.

Three main reasons for the withdrawal were identified: their fear to be unable to cope with an unfavorable
result, their better understanding of test implications after genetic counseling, and the protocol’s length.

Exclusions occurred during the first 4 years (Table 1) and 94.87% during the first 2 years. A total of 31 cases (39.74%) were excluded because they presented with unmistakable clinical signs of the disease, 26 cases (33.33%) because their psychological evaluations showed they were not able to handle unfavorable results at that moment and 21 cases (26.92%) because they did not belong to the SCA2 family.

In 2002 more than half of the total population entered the program (52.8%), but the highest number of withdrawals also occurred (81.37%). From 2003 to 2011 the highest level of adhesion to the program was achieved (92.62%).

Of the 768 individuals who completed the protocol, 223 (29.04%) had positive test results while 545 (70.96 %) had negative results ($\chi^2 = 135.00; p < 0.0001$).

Social and demographic characteristics of participants

The mean age at the time of testing was 37.24 years (range 13–88 years, SD 14.4 years; Fig. 2).

Females represented 59.77% of the sample for a male/female ratio of 0.67 ($\chi^2 = 29.30; p < 0.0001$). Most participants were living in partnership (73.05%), 79.17% of the individuals had a secondary school level or higher and 73.83% were non-religious (Table 2).

Family history

A maternal family history of SCA2 was present in 436 individuals (56.77%) and a paternal one in 332 (43.23%) ($\chi^2 = 14.08; p < 0.0001$).

Children before testing

Before testing, 46.62% of the individuals did not have offspring, 460 subjects (59.9%) wanted to have children while 308 (40.1%) did not, which was related to the number of previous offspring (Table 2): very few persons who had two or more children wanted to have another child (7 of 215), on the contrary, 98.32% of those without offspring would like to have some.

Among those who wanted to have children, a positive test result would have a determinant effect: 88.05% would request a PND, 9.35% would not have offspring, 1.3% would adopt a child, while 1.3% would take the risk and have offspring without performing a PND.

Table 1. Participants in the Cuban program for presymptomatic testing of spinocerebellar ataxia type 2 according to the uptake year and outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>%</th>
<th>Withdraw</th>
<th>% Exclusions</th>
<th>% Positive</th>
<th>% Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>103</td>
<td>9.8</td>
<td>13</td>
<td>6.37</td>
<td>12.82</td>
<td>13.9</td>
</tr>
<tr>
<td>2002</td>
<td>554</td>
<td>52.8</td>
<td>166</td>
<td>81.37</td>
<td>82.05</td>
<td>29.15</td>
</tr>
<tr>
<td>2003</td>
<td>47</td>
<td>4.5</td>
<td>4</td>
<td>1.96</td>
<td>2.56</td>
<td>9</td>
</tr>
<tr>
<td>2004</td>
<td>39</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
<td>2.56</td>
<td>15</td>
</tr>
<tr>
<td>2005</td>
<td>24</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>2006</td>
<td>9</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2007</td>
<td>24</td>
<td>2.3</td>
<td>1</td>
<td>0.49</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2008</td>
<td>64</td>
<td>6</td>
<td>4</td>
<td>1.96</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>2009</td>
<td>79</td>
<td>7.5</td>
<td>5</td>
<td>2.45</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>2010</td>
<td>61</td>
<td>5.8</td>
<td>8</td>
<td>3.92</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>2011</td>
<td>46</td>
<td>4.4</td>
<td>3</td>
<td>1.47</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>1050</td>
<td>100</td>
<td>204</td>
<td>100</td>
<td>78</td>
<td>223</td>
</tr>
</tbody>
</table>
The Cuban program for predictive testing of SCA2

Table 2. Social and demographic characteristics of participants in the Cuban spinocerebellar ataxia type 2 presymptomatic testing

<table>
<thead>
<tr>
<th>Presymptomatic testing</th>
<th>Male/female ratio: 0.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>162</td>
</tr>
<tr>
<td>Contract married/common-law</td>
<td>561</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>31</td>
</tr>
<tr>
<td>Widowed</td>
<td>14</td>
</tr>
<tr>
<td>Children before testing (wanting children)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>358 (352)</td>
</tr>
<tr>
<td>One</td>
<td>195 (101)</td>
</tr>
<tr>
<td>Two</td>
<td>145 (3)</td>
</tr>
<tr>
<td>More than two</td>
<td>70 (4)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>3</td>
</tr>
<tr>
<td>Primary school (1–6)</td>
<td>157</td>
</tr>
<tr>
<td>Secondary school (7–9)</td>
<td>230</td>
</tr>
<tr>
<td>Pre-university school (10–12)</td>
<td>258</td>
</tr>
<tr>
<td>Technician</td>
<td>44</td>
</tr>
<tr>
<td>University</td>
<td>76</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Religious</td>
<td>201</td>
</tr>
<tr>
<td>Non-religious</td>
<td>567</td>
</tr>
</tbody>
</table>

Reasons for taking the test

Most participants who completed the protocol expressed more than one reason for taking the test; their main motivations were: assessing the risk for their descendants (82.6%), preparing themselves physically and psychologically to cope with the disease (71.32%), planning for the future (61.44%), relieving the uncertainty (56.8%), informing and preparing their families regarding the disease (54.14%), family planning (42.77%), changing their lifestyle (14.24%), employment purposes (9.02%), and educational and career choices (5.69%).

Anticipated changes in response to the results of the test

The main anticipated changes in response to a positive result were: harm for their children (29.78%), emotional instability (16%), changes in their plans for the future (14.43%), familial conflicts (9.4%), job (7.32%) or career-related changes (6.19%) and dissolution of their marriage (2.31%). Besides, 0.5% of the participants expressed that ‘everything’ in their lives could be affected.

The majority of the consultands (95.61%) did not anticipate changes if the test result was negative, 1.83% anticipated emotional instability and less than 1% changes in their plans for the future, their marriage or the familial dynamics.

Possible changes were denied by the 18.25% of the participants, should the test result be either positive or negative.

To whom would they disclose the test results

In 72.4% of the cases they would disclose the result of the test to the same persons, either in a positive or a negative case, while in the rest the disclosure would depend on the result.

Additionally, 1.96% would not reveal the result to anyone in any case; 1.19% would reveal the result to everyone in every case and 1.96% would not disclose it to anyone when positive but would tell everyone when negative.

Among those willing to communicate their results, being the test result positive, they would share it with their partners (24.51%), their whole family (23.28%), their parents (19.98%), their children (16.66%) or everyone (19.22%). Being the test result negative 29.96% would tell everyone, 26.8% their whole family, 17.15% their partners, 12.41% their children and 13.24% their parents.

Discussion

This is the longest period of study of the Cuban national predictive program. The professionals are appropriately trained and possess the relevant competences to provide specialized attention; these are expected conditions in PST (16, 19). This is an outstanding circumstance to reflect our program’s strengths and shortcomings as well as how we could improve our practice.

Cuban peculiar profile of consultands at PST: reasons for uptake and withdrawal

First of all it is remarkable the number of individuals who requested their inclusion in the PST, which is related to the highest worldwide prevalence of SCA2 in Cuban population.

After 12 years with a predictive testing protocol for HD in Mexico, 11.5% of the at-risk individuals requested the test (20). In Montreal, Canada, there was an uptake of 9.2% in 15 years, which resulted lower in France (5%), Germany and Austria (3–4%) (21). In South Africa only 4.5% applied during 10 years (22). In general the uptake frequency has turned out to be lower than expected (23). In this way, Cuban uptake for predictive testing of SCA2 is larger than other predictive programs’ uptake for HD.

The adhesion to the SCA2 predictive protocol resulted similar to the one reported for HD in South Africa (75%) (22), Canada (74.58%) (21), and Germany (71%) (24). The percentage of withdrawal was also similar to Canada’s (22.1%) (21), resulting lower in Mexico (12%) (20) and South Africa (8.3%) (22), but higher in Brazilian (50%) (17) and Italian experiences (64%) (25).

The highest number of requests came about in the first 2 years of the program (2001 and 2002) (Table 1). The demand increased dramatically probably fuelled by the experience of the first participants, the high socioeducational level of the population, the free health care, and the health educational efforts in the
province (11). At the same time these families had longed for confirmatory molecular diagnosis of SCA2 as well as for predictive testing. Something similar happened in Canada, where applicants had been waiting for the direct mutation test of HD (21).

During this first period (2001 and 2002) the highest rate of exclusions and self-withdrawal also happened. Exclusions based on the psychological evaluations took place when consultands had a history of previous suicide attempt or severe psychiatric disturbances. When pathological levels of anxiety and/or depression were identified, psychological follow-up was offered in order to determine the proper time for them to take the test. Nevertheless none of them retried.

The withdrawal took place mainly after the first counseling session, this could mean that, being the test available, many applicants attended with enthusiasm but probably lacking sufficient knowledge about the test implications. Once genetic counseling was provided, they realized they were not ready to receive the information or to cope with a positive result.

From 2003, people got information about PST through the first participants’ experiences and genetic counseling actions, instead of educational campaigns. Since then, all families affected with SCA2 have been receiving personalized attention and genetic counseling at their communities, contributing this to the high pre-test knowledge level among participants in the PST and to the high level of adhesion to the program. The national training of genetic counselors in all municipalities of the country plays a remarkable role in health education of our population (13), and guarantees the delivery of genetic counseling services to every at-risk individual along the country.

In accordance with international findings, individuals with a negative test result were more frequent than individuals with a positive one (20–22). Brazil, on the contrary, reports rates of heterozygotes very similar to those observed in Mendelian segregation (51%), which could be in accordance with the hypothesis of a preferential transmission of expanded alleles over normal ones in SCA3 (17).

The mean age among participants in our and other predictive programs was similar (20–22, 24). Respecting sex distribution, female predominance has been observed in other predictive programs as well (17, 20, 21, 26). Explanation relies in their greater capability to face difficult decisions and their consequences, as well as their interest in family planning and in preventing the transmission of the disease to their descendants, together with the females’ assertive role in Cuban society (11).

Most participants in predictive programs live in a partnership (17, 20, 21); it was the same for our program.

Similar to the Montreal predictive program for HD (21), in our program almost half of the individuals did not have children before testing, representing a main motivation to take the test. Only a minority of them mentioned they would not have children were the test result positive. In Portugal, 61% of at-risk individuals for MJD living in the Azores, would not have children if they carried the mutation. Acceptance of PND and termination of pregnancy when confronted with a positive result for the fetus was low for this population (27, 28).

The main reason to participate in the SCA2 PST was not centred in the consultands but in the risk assessment for their descendants. This result is influenced by the majority of participants taking the test during the first 2 years of the program, most of them having already satisfied their reproductive needs and more focused on the risk for their offspring than for themselves. This represents a point of interest in clinical practice for genetic counseling, owing to the influence of motivational aspects during the counseling process. In our opinion, it is important to acknowledge all motivations involved in the decision-making process trying to focus participants on their own motivations while deciding to take the PST.

The denial of changes irrespective of the test result coming from some of the participants, together with the lack of anticipated changes in the majority of participants in the case of a negative result, are interesting findings, because there exist potential negative consequences of genetic testing that are vastly discussed during genetic counseling sessions (26, 29).

The disclosure of genetic information is one of many issues that may bring about ethical challenges (30). A low percent of the subjects would not disclose their results in any case or would not disclose them when positive. This behavior, although infrequent in our population, is probably determined by anticipated prejudices and by fear to social stigmatization. Some experiences are known where affected patients have been mistaken with ‘drunken people’ because of the ataxic gait and the dysarthric speech, thus receiving an inadequate treatment by others.

In regard to disclosing the results, it should be considered that a negative result is a different scenario than a positive one. Individuals in the former situation would tell everyone, then their family, then their partners; while individuals in the latter case would disclose the results to their partners or to some family members and lastly to everyone. This reinforces the previous idea of fear to share a positive result or at least, the need of time, or even some professional help, in order to be prepared to share their new genetic status with others.

Internationally, most individuals find predictive testing experience to be satisfactory, regardless of the test result (11, 12, 17, 20, 21, 31). Nevertheless, testees may need years to adapt to their genetic status, whichever this might be; therefore PST impact needs to be valued from a life-cycle perspective (26) and professional and community resources are necessary to deal with the psychological burden of PST (27).

Again, the role of genetic counselors and other health professionals at the community level should be highlighted, considering that the long-term impact is more and more a community issue. Undoubtedly, this always depends on the crucial ethical point
related to what extent the experience of being tested is shared with the primary health professionals, the family members and other community stakeholders, especially if we take into account that some individuals keep their participation in the program exclusively to their own.

Conclusions
The profile of Cuban participants in the predictive testing program is similar to the one reported for other programs all over the world, nevertheless genetic counseling practice at the community level is a distinctive aspect, which is valuable in providing at-risk individuals with wide and proper knowledge before their testing inclusion request.

The SCA2 PST program has high uptake rates and is renowned in our population, this having important implications for the future practice, because programs for the predictive diagnosis of neurodegenerative conditions (such as HD and other hereditary ataxias) could also be developed in our country, broadening our diagnostic capabilities.

Our program is nevertheless in debt with the assessment of the long-term psychological impact in the participants, their partners and relatives, as well as with the study of those at-risk family members who decided not to be tested. Longitudinal studies focused on consultands’ experiences and family aspects surrounding the uptake and impact of PST are needed. Future research will also focus on refining the boundaries limiting the ending of the presymptomatic stage, as well as in developing clinical trials aimed at delaying as much as possible the beginning of the disease in presymptomatic subjects.

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References


