Cambodian founder effect for spinocerebellar ataxia type 3 (Machado–Joseph disease)

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Abstract

Four families from the same region of Cambodia immigrated to the Pacific Northwest of the United States. All four families have been discovered to have spinocerebellar ataxia type 3 (SCA 3; Machado–Joseph disease) with a similar clinical phenotype. CAG repeat expansions in the ATXN3 gene range from 72 to 77. Mean age of onset has varied from 19 to 44 years and mean age at death of 4 individuals has been 60 years. The prevalence of the various subtypes of SCA varies worldwide from country to country. Neurologists should be alert to the possibility of SCA 3 in Cambodian patients with unexplained cerebellar ataxia.

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1. Introduction

The autosomal-dominant inherited spinocerebellar ataxias (SCA) now number 28 at the time of this report [1,2]. The prevalence of each type varies from country to country and even from region to region. For example, SCA 8 is the most common type in Finland [3] whereas SCA 3 (Machado–Joseph disease) is the most common type in the United States [2]. In Japan, SCA 3 is relatively common, but it is uncommon in the region of Nagano [4].

As noted by Zhao [5], relative to the West, there is a paucity of information about SCA in Asian countries. Especially little is known about the prevalence of SCA in Southeast Asia. We report here several families of Cambodian origin with SCA 3 and provide evidence for a founder effect in this ethnic group. We also review the known frequencies of SCA 3 in Asian countries.

2. Families

All four families originated from different villages and towns in the northwest region of Cambodia near the border with Thailand (Fig. 1). The pedigree of Family A is shown in Fig. 2. The clinical and molecular characteristics of the families are summarized in Table 1. The proband (II-4) of Family A developed unsteady gait at age 39 followed by slowly progressive ataxia associated with horizontal jerk nystagmus, paralysis of upgaze, hyperactive tendon-reflexes and decreased vibratory sensation in the feet. He died of pneumonia at age 62. He had 75 CAG repeats in the ataxin-3 gene (ATXN3; repeat expansion detected by previously described methods [6]). His two daughters have had earlier onset at ages 19 and 25 years with 77 and 76 CAG repeats, respectively (III-11, 13). Both his sons are affected on examination but have not yet undergone DNA testing. In addition to ataxia, one of his daughters (III-13) has had prominent fasciculations of facial muscles associated with trismus of her jaw treated with Botoxulim toxin injections. The family has had 9 affected individuals over three generations. Only family member II-4 had paralysis of upgaze...
and only III-13 had trismus of the jaw. No family member has had cognitive decline.

Family B (Table 1) is an affected pair of sisters with onset at 25 and 39 years of age with ataxia, dysarthria, nystagmus, poor upgaze, hypoactive tendon reflexes and normal sensation.

Family C (Table 1) includes a man with onset at age 38 whose affected mother died in Cambodia. He has ataxia, dysarthria, nystagmus, a right 6th cranial nerve palsy and hyperactive tendon reflexes with Babinski signs.

Family D (Table 1) is represented by a man with onset of ataxia at age 44 whose affected father died in his forties. This man has ataxia, nystagmus, restricted eye movements, hyperactive tendon reflexes, and fasciculations of tongue and eyelids.

CT and MRI imaging early in the disease of persons in these families have either been normal or shown mild cerebellar atrophy.

3. Discussion

The phenotype demonstrated in the families reported here is typical of the wide variety of clinical manifestations seen
in SCA 3. These clinical characteristics sometimes include pyramidal tract signs, brain stem abnormalities, and lower motor neuron findings in addition to ataxia. Onset of symptoms begins in the twenties to forties with anticipation associated with larger CAG repeat size. The importance of these families is their common ethnic background and country of origin (Cambodia).

The worldwide frequency of the various subtypes of autosomal dominant hereditary ataxia have been reviewed by Schols et al. [2]. SCA 3 is the most common type overall with a frequency of about 21%. Outside of Asia the frequency of families with SCA 3 varies from a high of more than 60% in Portugal and Brazil to a low of less than 5% in South Africa and no cases found in a Czech population [7,8]. SCA 3 represents about 20% of autosomal dominant ataxias in the United States.

Table 2 shows the available reports describing the frequency of SCA 3 in 7 different Asian countries. The frequency (as a percentage of families with autosomal dominant ataxia) varies from a high of 49% in China to a low of 5% or less in India. It is noted that even within a single country such as Japan there may be a considerable variety in the frequency ranging from 24% in the Kinki and Hokkaido areas to 3% in Nagano. These differences are also likely to represent the proportion of various founder families with specific ataxia subtypes.

The reason for the unusually high frequency of SCA 3 in Portugal and Brazil is the result of a founder effect that was first noticed in descendants from the Portuguese Azores Islands and originally called Machado–Joseph disease (MJD). Linkage disequilibrium analysis suggests two distinct mutational events on the background of different haplotypes have occurred in the Portuguese population. The expansion associated with the ACA haplotype accounts for a majority (72%) of MJD families worldwide [9]. Interestingly, the ACA frequency in the general Portuguese population is quite low (2%) and is the least common haplotype in controls. Investigation into the ancestral origins of MJD in non-Azorean families confirmed the ACA haplotype predominance in Indian SCA 3 cases [10]. However in India, in contrast to the Portuguese population, ACA is very common in normal alleles (40%), being associated with larger normal alleles (>26 CAG repeats) that may have been prone to expansion [10].

Thus, while the pathogenic repeat occurring on the ACA haplotype may have been the source of a worldwide founder effect, the original origins of the ACA haplotype may have been outside Portugal and imported into the Portuguese and Azorean population after European–South East Asian intermingling that began in the 1400s.

During Portugal’s trading ventures throughout Southeast Asia in the 1500–1600s, a Portuguese presence in the form of merchants, mercenaries and missionaries was found in Cambodia [11,12]. It is possible that introduction of the MJD

### Table 1
Cambodian families with SCA 3

<table>
<thead>
<tr>
<th>Family</th>
<th>Onset age</th>
<th>CAG repeat number</th>
<th>Ataxia</th>
<th>Tendon reflexes</th>
<th>Eye movements</th>
<th>Dysarthria</th>
<th>Sensation</th>
<th>Facial fasciculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-4</td>
<td>39</td>
<td>75</td>
<td>+</td>
<td>↑</td>
<td>abnl</td>
<td>−</td>
<td>↓</td>
<td>−</td>
</tr>
<tr>
<td>II-5</td>
<td>41</td>
<td>73</td>
<td>+</td>
<td>nl</td>
<td>abnl</td>
<td>+</td>
<td>↓</td>
<td>−</td>
</tr>
<tr>
<td>III-8</td>
<td>36</td>
<td>unk</td>
<td>+</td>
<td>+</td>
<td>nyst</td>
<td>−</td>
<td>nl</td>
<td>+</td>
</tr>
<tr>
<td>III-11</td>
<td>25</td>
<td>76</td>
<td>+</td>
<td>↑</td>
<td>abnl</td>
<td>−</td>
<td>nl</td>
<td>+</td>
</tr>
<tr>
<td>III-12</td>
<td>22</td>
<td>unk</td>
<td>+</td>
<td>+</td>
<td>nyst</td>
<td>+</td>
<td>nl</td>
<td>+</td>
</tr>
<tr>
<td>III-13</td>
<td>19</td>
<td>77</td>
<td>+</td>
<td>↑</td>
<td>nyst</td>
<td>+</td>
<td>nl</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>39</td>
<td>72</td>
<td>+</td>
<td>↓</td>
<td>abnl</td>
<td>+</td>
<td>nl</td>
<td>−</td>
</tr>
<tr>
<td>C</td>
<td>38</td>
<td>72</td>
<td>+</td>
<td>↑</td>
<td>abnl</td>
<td>+</td>
<td>nl</td>
<td>−</td>
</tr>
<tr>
<td>D</td>
<td>44</td>
<td>75</td>
<td>+</td>
<td>↑</td>
<td>abnl</td>
<td>−</td>
<td>nl</td>
<td>+</td>
</tr>
</tbody>
</table>

↑ = increase.
↓ = decrease.
+ = present.
− = absent.
nl = normal.
abnl = abnormal.
unk = unknown.
nyst = nystagmus.

### Table 2
Frequency of SCA 3 in Asian countries

<table>
<thead>
<tr>
<th>Country</th>
<th>District</th>
<th>SCA 3 (% of AD ataxia families)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>Nagano</td>
<td>27.6</td>
<td>Manuyama et al. [13]</td>
</tr>
<tr>
<td></td>
<td>Kinki</td>
<td>3.0</td>
<td>Shimizu et al. [4]</td>
</tr>
<tr>
<td></td>
<td>Hokkaido</td>
<td>24.0</td>
<td>Matsumura et al. [14]</td>
</tr>
<tr>
<td>China</td>
<td></td>
<td>48.0</td>
<td>Sasaki et al. [15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>49.2</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
<td>32.0</td>
<td>Tsai et al. [19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47.3</td>
<td>Soong et al. [20]</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td>5.0</td>
<td>Saleen et al. [21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6</td>
<td>Srivastava et al. [22]</td>
</tr>
<tr>
<td>Korea</td>
<td>Suwon</td>
<td>15.0</td>
<td>Bang et al. [23]</td>
</tr>
<tr>
<td></td>
<td>Seoul</td>
<td>29.0</td>
<td>Lee et al. [24]</td>
</tr>
<tr>
<td>Cambodia</td>
<td></td>
<td></td>
<td>This report</td>
</tr>
<tr>
<td>Singapore/ Malaysia</td>
<td></td>
<td>42.0</td>
<td>Zhao et al. [5]</td>
</tr>
</tbody>
</table>
mutation occurred at that time. However, in the absence of firm molecular or historical confirmation, that remains speculative.

The present families demonstrate an SCA 3 founder effect has probably occurred in Cambodia. The four families reported here all came from the same northwest region of Cambodia and are likely to be distantly related. DNA was not available to perform a haplotype analysis of our families in this report to further document this hypothesis. The one Cambodian SCA 3 family that was studied in a recent haplotype analysis carries the pathologic CAG repeat expansion on the ACA haplotype [9].

As a practical point, the present report supports the notion that SCA 3 should be an important part of the differential diagnosis in any patient of Cambodian ethnic origin who presents with unexplained ataxia. The large number of immigrants from Southeast Asia to the United States and Canada suggests that additional such families will be seen in North America.

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References


