Hereditary spinocerebellar ataxias: number, prevalence, and treatment prospects

The autosomal dominant spinocerebellar ataxias (ADSCA) are a group of late-onset neurodegenerative disorders. Since the elucidation of the genetic basis of these disorders, the clinical term ADSCA has been replaced by that of spinocerebellar ataxias (SCAs). In most families with SCA, progressive ataxia is not isolated but occurs in combination with a variety of other neurological features—a finding that suggests extra-cerebellar involvement. In pathological terms, SCAs are characterised by the degeneration of the cerebellum, brainstem, and their efferent or afferent nerve fibres.

How many subtypes are there exactly?

Genetic heterogeneity of the SCAs has been well established. So far, 25 genetic loci have been mapped: SCA1 to 8, SCA10 to 19, SCA21 to 25, fibroblast growth factor 14 (FGF14)–SCA, and dentatorubropallidolysian atrophy (DRPLA). Twelve of the corresponding genes (SCA1, 2, 3, 6, 7, 8, 10, 12, 14, and 17, FGF14-SCA and DRPLA) have been cloned. The main defect in seven of these genes (SCA1, 2, 3, 6, 7, and 17, and DRPLA) is an expanded repetition of a nucleotide triplet that encodes for glutamine (CAG). The accumulation of polyglutamine in the cytoplasm and nucleus in turn damages neurons in the central nervous system. A similar pathological mechanism is responsible for Huntington’s disease (HD) and spinobulbar muscular atrophy. Trinucleotide repeat expansion may also occur for Huntington’s disease (HD) and spinobulbar muscular atrophy.

International prevalence estimates of SCA vary from 0.3 to 3.0 per 100 000. However, the relative frequencies of some genetically defined SCAs vary significantly according to race and place of birth, presumably due to founder effects (ie the difference between the gene pool of a population as a whole and that of a newly isolated population of the same species): SCA2 among Cubans; SCA3 among people born in the Azores, Portugal; and SCA10 among Mexicans.

In Japan, SCA6, SCA3 (or Machado-Joseph disease [MJD]), and DRPLA are the three major disorders, whereas SCA7, 8, 10, 12, and 17 are infrequent or almost undetected. However, SCA1 occurs predominantly in the northern part of Japan. An apparent difference in the prevalence of each SCA may be attributable to the historical and regional difference in the distribution of inhabitants.

In Singapore, Zhao et al found that the estimated prevalence of SCA among Singaporean families was at least 1 in 27 000. On the basis of history and ancestry, the researchers observed a founder effect for specific SCA subtypes, as well as an association between ethnicity and SCA subtype. In a study of families from Mainland China, Tang et al reported that the prevalence of SCA3/MJD was substantially higher than that of SCA1 and SCA2 in patients with ADSCA. And Soong et al found that SCA3/MJD was the most common type of ADSCA in Taiwan (47.3%), followed by SCA6 (10.8%), SCA2 (10.8%), SCA1 (5.4%), SCA7 (2.7%), SCA8 (2.7%), and DRPLA (1.4%). The genes responsible for 21.6% of dominantly inherited SCA cases remain unidentified. Among patients with sporadic ataxias in Taiwan, 4.1% were found to harbour SCA6 mutations.

Although SCA6 has, so far, not been reported in Mainland China, a geographical cluster of families with SCA6 has been reported in the Chinese population in Taiwan. In the majority (70%) of these patients with SCA6, genotyping revealed a shared allele of a marker within the CACNL1A4 gene. Together with the geographical clustering of the families with SCA6, this observation seems to support the hypothesis of a founder effect. Similar geographical clusters of SCA6 have also been observed in the Chugoku area of western Japan, the Northrhine-Westfalia area of Germany, and in the northeast of England.

In this issue of the Hong Kong Medical Journal, Lau et al reported their findings of molecular and clinical studies of SCA from three regional hospitals—the first investigation of its kind among a Chinese population in Hong Kong. By studying 14 families, they detected mutations in SCA1, SCA3, and DRPLA genes. Of note is that previously, there had been only one DRPLA pedigree reported among the Chinese population worldwide. Moreover, most other affected family members of those SCA pedigrees were unavailable for the study, and two of the index cases did not have a family history of ataxia. Hence, whether the instability of CAG repeats during meiosis results in ‘anticipation’ (earlier disease onset in subsequent generations) and the effect of parental sex on the number of CAG repeats in the next generation could not be investigated. Furthermore, because the sample size was fairly small (n=12), the relationship between the size of the CAG repeats and the age at onset of symptoms in SCA3 could not be reliably determined.
How soon will there be a treatment?

The gene for HD was cloned in 1993—earlier than most of the SCA genes—and many drug trials have been undertaken for HD. Because HD and many SCAs share similar pathological mechanisms, people have been hoping that therapies that are effective in treating HD might also work for at least some SCAs. Many drug trials have been conducted in animals, but few drugs that show promise in animals ever advance to human studies. For example, Steffen et al demonstrated that therapy with histone deacetylase inhibitors might slow or prevent the progressive neurodegeneration seen in Drosophila models of HD and of other polyglutamine-repeat diseases, even after the onset of symptoms. Tanaka et al demonstrated that trehalose could effectively reduce the accumulation of polyglutamine in the brains of mice with HD and improve motor dysfunction and increase lifespan. The technique of RNA interference has also been found to halt the progress of dominant neurogenetic disorders. Finally, the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, US, has launched a rigorous project called “the Systematic Evaluation of Treatments for Huntington’s Disease.” Two hundred potential compounds have been nominated that could help patients. Perhaps, after all, this approach will yield more drug candidates than conventional clinical trials so far have.

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References