SCA3: Neurological features, pathogenesis and animal models

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Abstract
The most frequent subtype of autosomal dominant inherited spinocerebellar ataxias is caused by CAG repeat expansions of more than 55 units in the ataxin-3 gene. The clinical variability of the phenotype depends on the length of the expanded repeat and the age at onset (and thus indirectly with the repeat size). Anticipation of the phenotype is most frequently associated with repeat expansions in paternal transmission. In this review we describe four clinical subphenotypes and correlate them to the respective repeat expansions. We also provide a detailed description of the neuropathological features. Finally, we discuss the current knowledge on the function of normal and dysfunction of altered ataxin-3 and how this translates to the predicted structure of the protein.

Key words: Spinocerebellar ataxia 3, Machado-Joseph disease, ataxin 3, polyglutamine disease, mosaicism

Introduction
Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is the most frequent form among the autosomal dominantly inherited cerebellar ataxias in Europe, Japan, and the United States (1,2). SCA3 belongs to the group of polyglutamine repeat (polyQ) diseases as SCA1, 2, 6, 7, and 17, dentatorubro-pallidoluysian atrophy (DRPLA), spinobulbar muscular atrophy (SBMA), and Huntington’s disease (HD). As in most of these polyglutamine diseases, patients with a repeat expansion in the SCA3 gene form intranuclear aggregates and neuronal cell loss in selected areas of the brain. Herein, we will summarize characteristic features of SCA3, which are common to polyQ diseases and describe specific features which are unique to SCA3. We also review the current knowledge on protein function and structure.

Genetic causes of SCA3 and population genetics
The SCA3 gene has been mapped to the long arm of chromosome 14 (3). Screening of a human brain cDNA library for genes containing CAG repeats revealed a novel gene (MJD1) of 1,776 bp with at that time unknown function which mapped to the 14q32.1 region (4). Screening for CAG repeat expansions in 12 Japanese SCA patients with clinical signs of MJD revealed a repeat expansion from 68 to 79 CAGs in 11 of the patients whereas 72 healthy Japanese controls harboured between 13 and 36 repeats (4). A large number of genetic studies over the last 12 years finally: (i) defined the normal range of CAG repeats in the MJD1 gene up to 47 (5), (ii) and the expanded repeat size of more than 44 (6) with 86 being the largest expanded repeat described (7), (iii) revealed that MJD is genetically identical to SCA3 (1,8–10), (iv) indicated that the expanded CAG repeat is widely unstable during paternal transmission, (v) showed evidence for somatic mosaicism of the expanded allele, and (vi) that besides the expanded CAG repeat length additional genetic factors exist manifesting the age at onset of SCA3.

Ad 1
Normal repeat size: there is an overlap of normal repeat sizes (up to 47, (5)) with the smallest expanded repeat of 45 CAGs (6). As has been shown for other polyQ diseases (HD, (11)) individuals with a repeat length in the overlapping region do not always manifest with the disease (reduced penetrance). However, similarly to other CAG
repeat diseases, the repeat is not a pure CAG stretch and variant CAA (third and sixth position) and AGG (fourth position) triplets are found in the normal alleles (4).

Ad 2

Expanded CAG repeats and frequency: MJD is thought to have originated from founders in the Iberia Peninsula, who migrated to the Azores and then to several other countries including Japan and America. However, based on haplotype studies characterizing polymorphisms flanking the MJD1 gene there is striking evidence for independent and multiple origin of MJD/SCA3 in different populations (12,13) although the majority of the families may be derived from one founder mutation (14). In sporadic cerebellar ataxias repeat expansions in the MJD1 gene are barely found (15,16). The shortest known expanded CAG repeat in the MJD1 gene carries 45 expanded repeats which occurred in an Indian family with clinical features of SCA and brainstem atrophy on MRI scan (6). Even at this small expanded size the repeat was unstable upon inter-generational transmission. In another Japanese patient, 56 units have been found in a patient cerebellar ataxia and autonomic dysfunction at the age of 51 years and a family history of unsteadiness in gait (17). Interestingly, the mutant allele is preferentially transmitted in male meiosis in Japanese MJD patients (18) whereas we found for the German population a preferential transmission of the repeat expansion by female carriers (19).

Ad 3

Machado-Joseph disease was initially described in emigrants from the Azorean islands Sao Miguel (Machado family) and Flores (Joseph family) (20,21). The ‘Azorean disease’ was characterized by dominant inheritance and cerebellar ataxia in variable combination with pyramidal signs, dystonic-rigid syndrome or peripheral neuropathy. Progressive external ophthalmoplegia, dystonia, intention facial and lingual fasciculation-like movements and bulging eyes were regarded as more specific signs of the disease (22). MJD was rarely encountered in ethnic groups other than Portuguese before cloning the responsible gene. Straightforward genetic testing of large cohorts of ataxia patients revealed frequent repeat expansions in the MJD1 4 gene in many populations and demonstrated MJD to be the most frequent type of dominant ataxia worldwide (reviewed in (2)). Interestingly, many patients do not prominently present characteristic features of MJD and were therefore described as SCA3. Finally, genetic testing definitely demonstrated that MJD and SCA3 are allelic disorders (1,8,9).

Ad 4

Intergenerational instability: in SCA3 intergenerational instability is more prominent in paternal than in maternal transmission (23,24). Larger expanded CAG repeat sizes are indirectly correlated with the age at onset in SCA3, which is known as anticipation. Thus, there is a higher risk for earlier manifestation of the disease in children from affected fathers. Interestingly, a CGG/GGG polymorphism at the 3'-end of the CAG repeat affects intergenerational instability. A combination of paternal transmission and [expanded (CAG)n-CGG]/[normal (CAG)n-GGG] haplotypes results in a 75-fold increased relative risk compared with that of maternal transmission and [expanded (CAG)n-CGG]/[normal (CAG)n-CGG] or [expanded (CAG)n-GGG]/[normal (CAG)n-GGG] haplotypes suggesting interallelic effects on CAG repeat stability (25,26). Furthermore, this (CAG)n-CGG variation was not found in alleles with less than 20 CAG repeats (27) supporting the hypothesis that this polymorphism may be associated with CAG repeat instability.

Ad 5

Somatic mosaicism of the repeat sizes in CAG repeat disorders describes that different cells of the same individual carry different repeat sizes. This phenomenon has never been described for the normal repeat length, but it has been observed for several polyQ diseases such as HD, DRPLA, and SCA1 (28–30). Somatic instability has also been described for SCA3 in different brain areas (31) with smaller expanded repeat sizes in the cerebellar cortex than in other brain regions such as the frontal cortex (32).

Ad 6

Genetic modifiers: although it has been shown that the expanded CAG repeat size predicts largely the age at onset in SCA3 with correlation factors ranging from −0.67 to −0.87 (1,4,23,24) it is evident that CAG repeat length does not account for all of the variation. Also, the variance of the age at onset in SCA3/MJD patients with similar expanded CAG repeat sizes suggested that additional factors influence the age at onset. Although to our knowledge no such environmental factor has been defined yet as has been for HD or Parkinson’s disease for instance, it can be predicted that a healthy life style leads to a later disease manifestation in SCA3 as well. However, other genetic factors besides the CAG repeat are thought to modify the age at onset. As such it has been shown that females manifest later in life as their brothers even with the same expanded repeat size or longer normal CAG repeat sizes (Kawakami et al. 1995) although a gender influence has not been confirmed by others (33,34). Positive correlations were also observed for avuncular (r=0.22) and