AR Gene Analysis for Spinal and Bulbar Muscular Atrophy

CLINICAL FEATURES

Spinal and bulbar muscular atrophy (SBMA) is a slowly progressive neuromuscular disorder in which degeneration of the lower motor neurons causes muscle weakness, muscle atrophy, and fasciculations of the perioral region. The onset of disease ranges from 18-64 years of age, with most individuals presenting in the fourth or fifth decade.[1] Androgen insensitivity, resulting in gynecomastia, testicular atrophy, and oligospermia/azoospermia, can present in adolescence.[2] The onset of neurological symptoms typically ranges from 30-50 years of age; features can include muscle cramps, active tremor, decreased deep tendon reflexes, difficulty walking, and frequent falls due to muscle weakness.[2] As the proximal and distal weakness and atrophy progresses, ambulation becomes more difficult. Bulbar muscle involvement typically progresses early in the fifth decade resulting in difficulties in articulation (dysarthria) and difficulty swallowing (dysphagia).[3] In a minority of individuals with SBMA there is a risk for potentially life-threatening aspiration pneumonia and respiratory failure as a result of weakness in the bulbar and respiratory musculaturature.[3,4] Histopathology findings include degeneration of motor neurons in the spinal cord and brainstem, and the identification of nuclear inclusions containing abnormal androgen receptor protein in the remaining motor neurons.[5, 6, 7] Electromyography (EMG) findings include anterior horn cell loss, sensory neuropathy, and diffuse denervation atrophy.[8] The prevalence of SBMA is estimated at 1:40,000-1:50,000 males, with a higher prevalence in European and Asian populations.[2,]

GENETICS

SBMA is inherited in an X-linked manner. It is caused by expansion of the glutamine repeat (CAG) in exon 1 of the androgen receptor (AR) gene.2 Normal alleles have 34 or less CAG trinucleotide repeats, and disease alleles have 38 or more repeats . [1,3] Reduced penetrance has been observed in families with alleles that have 35-37 repeats. In those individuals that have alleles within the reduced penetrance range, clinical significance should be interpreted within the context of the individual's clinical presentation and family history.[2] There is an inverse correlation between CAG repeat length and age of onset, as well as a direct correlation between repeat length and disease severity.[3,9] The glutamine repeat in AR is meiotically unstable, leading to expansion of the repeat during transmission from parent to offspring. While a correlation exists between repeat number and disease onset and severity, prediction of disease course cannot be based solely on the repeat number.[10]

TEST METHODS

Using genomic DNA obtained from the submitted specimen, repeat analysis is performed via standard PCR fragment analysis to determine the number of repeats in each allele. Nucleotide repeat numbers up to 50 are reported with an accuracy of +/- 2 repeats and repeat numbers >50 are reported with an accuracy of +/- 5 repeats. The exact number of repeats cannot be determine for alleles with >75 repeats. Internal standards are analyzed along with clinical samples to evaluate assay performance. The largest recorded allele of 78 repeats can be analyzed accurately using this strategy alone.

CLINICAL SENSITIVITY

The clinical sensitivity for analysis of the glutamine repeat in AR depends on the clinical phenotype of the patient. All individuals with SBMA have an expansion of the glutamine repeat in exon 1 of the AR gene, which is detectable by this targeted mutation analysis[8]. The technical sensitivity of fragment analysis is estimated to be greater than 95%. Pathogenic single nucleotide variants and whole or partial deletions and duplications of the AR gene are not reported in association with SBMA and would not be detected by this analysis.

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