Very Late Onset in Ataxia Oculomotor Apraxia Type I

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Missense and truncating mutation in *APTX* gene are responsible of ataxia with oculomotor apraxia type 1 (AOA1) an autosomal recessive disorder characterized by early onset, progressive ataxia, peripheral neuropathy, oculomotor apraxia, and cerebellar atrophy.[1,2] We have already reported two patients with onset at 25 and 29 years suggesting that AOA1 should be considered in patients with onset after 25 years.[3] Here, we report a patient with a very late onset and a new mutation further expanding the clinical and molecular spectrum of the disease.

The coding sequence of *APTX* was analyzed using denaturing high-performance liquid chromatography in 15 index cases selected among 90 sporadic late-onset non–Friedreich ataxia (FRDA) patients. The inclusion criteria were onset between 25 and 50 years, sporadic occurrence, and clinical and/or neurophysiological signs of peripheral neuropathy. *APTX* analysis showed a new homozygous 6668T→C mutation (exon 5) in one patient, resulting in the substitution of proline for leucine at codon 223 (L223P). Onset of the disease was at age 40 years with ataxia followed by dysarthria. Neurological examination showed mild gait and limb ataxia, slurred speech, dysphagia, normal ocular movements, tongue and limb fasciculations, brisk jaw jerk, areflexia, and decreased vibration sense at the external malleoli. Normal serum creatine kinase and albumin, mild familial hypercholesterolemia, and hypertrigliceridemia were observed.

Motor (47m/sec in the elbow-wrist segment; lower limit 54) and sensory (43.3 m/sec in the digit III–wrist segment; lower limit 51) conduction velocities were slightly decreased at the median nerve, and sensory action potential was markedly reduced at wrist (1.8 μV; lower limit 6). Electromyogram showed a neurogenic pattern in the anterior tibial muscle. Brain magnetic resonance imaging showed cerebellar atrophy. After 20 years of disease, the patient walks without supports and is still working, and only speech is significantly worsened. These findings suggest that the new mutation is associated with a peculiarly mild phenotype. Homology modeling calculations performed for aprataxin and its L223P mutant showed that H166-F282 sequence is compatible with a HIT-like domain for both proteins (Fig). However, the P223L substitution falls in the middle of an α-helix, and proline is known to have a low propensity for an α-helix formation. Thus, such a point mutation may lead to some destabilization of the protein fold. L223P is not present in the healthy brother, is conserved in human (Gene Bank accession number AY040777) and mouse (NM175073), and was absent in 150 southern Italian controls.

We emphasize the potential pitfall when selecting only patients with early onset for *APTX* screening. The identification of patients with preserved knee jerks suggests also that neuropathy is inconstant.[4] To date, mutations have been found only in the last three *APTX* exons. Thus, the screening of such exons could be useful in sporadic or recessive patients with cerebellar atrophy, after exclusion of FRDA.

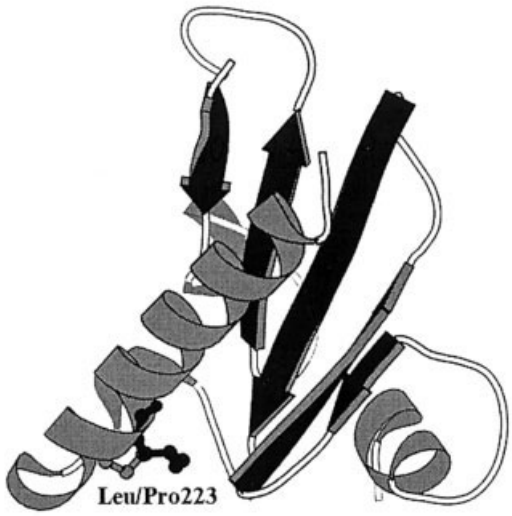

Fig. Superposition of the overall fold of the homology models built for H166-F282 aprataxin and its L223P mutant with 3D-PSSM software.[5] α-Helices and β-strands are represented in gray and black, respectively. The alignment between H166-F282 sequence and the template (protein kinase C inhibitor–1; pdb code = 1kpf) shows short deletions only in loop regions.

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High Endogenous Cannabinoid Levels in the Cerebrospinal Fluid of Untreated Parkinson's Disease Patients

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Endocannabinoids are a class of bioactive lipids responsible for the activation of type 1 (CB1) and type 2 (CB2) cannabinoid receptors. A close functional interaction between

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