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## Research Article

# The novel human gene aprataxin is directly involved in DNA single-strand-break repair

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**Abstract.** The cells of an ataxia-oculomotor apraxia type 1 (AOA1) patient, homozygous for a new aprataxin mutation (T739C), were treated with camptothecin, an inhibitor of DNA topoisomerase I which induces DNA single-strand breaks. DNA damage was evaluated by cytogenetic analysis of chromosomal aberrations. The results obtained showed marked and dose-related increases in induced chromosomal aberrations in the patient and her heterozygous mother compared to the intrafamilial wild-type control. The alkaline comet assay confirmed this pattern. Moreover, the AOA1 cells did not show hypersensitivity to ionizing radiation, i.e. X-rays. These findings clearly indicate the direct involvement of aprataxin in the DNA single-strand-break repair machinery.

**Key words.** DNA single-strand-break repair; aprataxin; chromosomal aberration; camptothecin; inhibitor of DNA topoisomerase I.

Mutations of aprataxin (APTX), a novel human gene located in the 9p13 region, have been recently linked by two independent reports [1, 2] to ataxia-oculomotor apraxia type 1 (AOA1), an autosomal recessive syndrome characterised clinically by early onset cerebellar ataxia, oculomotor apraxia and late peripheral neuropathy. The same neurological features characterise ataxia telangiectasia (AT), another rare human autosomal recessive disorder also presenting with extreme sensitivity to ionising radiation (IR) and susceptibility to cancer, immunodeficiency, oculocutaneous telangiectasias, progressive neurodegeneration, growth retardation, developmental abnormalities and premature ageing [3–6]. The ATM gene, defective in AT patients, determines cellular responses for the recognition and processing of DNA double-strand breaks induced by IR and DNA-alkylating agents [7]. AOA 1, however, is not sensitive to IR and does not show cancer proneness and genomic instability but is, rather, characterised by enhanced sensitivity to agents that cause DNA single strand breaks [8].

The APTX gene encodes a nuclear protein considered to be a member of the Hint (histidine-triad-nucleotide-binding) subfamily of the histidine triad (HIT) domain. These proteins are nucleotide hydrolases and transferases exhibiting approximately 30% homology with the active site of human and rabbit Hint1 which binds nucleotides and displays adenosine 5′-monophosphoramidase activity [9]. Althongh the structure and biochemical activities of these proteins have been fully described, their biological roles are still unknown. Similarly, nothing is known about the cellular involvement of aprataxin in preventing neurodegeneration in AOA1 patients.

In addition, there is a region of homology between the amino terminus of aparataxin and that of human PNK, a

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