

Functional classification of ATM variants in ataxia-telangiectasia patients

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Abstract

Ataxia-telangiectasia (A-T) is a recessive disorder caused by biallelic pathogenic variants of ataxia-telangiectasia mutated (ATM). This disease is characterized by progressive ataxia, telangiectasia, immune deficiency, predisposition to malignancies, and radiosensitivity. However, hypomorphic variants may be discovered associated with very atypical phenotypes, raising the importance of evaluating their pathogenic effects. In this study, multiple functional analyses were performed on lymphoblastoid cell lines from 36 patients, comprising 49 ATM variants, 24 being of uncertain significance. Thirteen patients with atypical phenotype and presumably hypomorphic variants were of particular interest to test strength of functional analyses and to highlight discrepancies with typical patients. Western-blot combined with transcript analyses allowed the identification of one missing variant, confirmed suspected splice defects and revealed unsuspected minor transcripts. Subcellular localization analyses confirmed the low level and abnormal cytoplasmic localization of ATM for most A-T cell lines. Interestingly, atypical patients had lower kinase defect and less altered cell-cycle distribution after genotoxic stress than typical patients. In conclusion, this study demonstrated the pathogenic effects of the 49 variants, highlighted the strength of KAP1 phosphorylation test for pathogenicity assessment and allowed the establishment of the Ataxia-TeLangiectasia Atypical Score to predict atypical phenotype. Altogether, we propose strategies for ATM variant detection and classification.

Keywords: ataxia-telangiectasia; ataxia-telangiectasia mutated (ATM); checkpoint; mutation; phenotype; splice.