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Two novel mutations associated with ataxia-telangiectasia identified using an ion ampliSeq inherited disease panel

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Abstract

© 2017 Kuznetsova, Trofimov, Shubina, Kochetkova, Karetnikova, Barkov, Bakharev, Gusev and Sukhikh. Ataxia-telangiectasia (A-T), or Louis-Bar syndrome, is a rare neurodegenerative disorder associated with immunodeficiency. For families with at least one affected child, timely A-T genotyping during any subsequent pregnancy allows the parents to make an informed decision about whether to continue to term when the fetus is affected. Mutations in the ATM gene, which is 150 kb long, give rise to A-T; more than 600 pathogenic variants in ATM have been characterized since 1990 and new mutations continue to be discovered annually. Therefore, limiting genetic screening to previously known SNPs by PCR or hybridization with microarrays may not identify the specific pathog enic genotype in ATM for a given A-T family. However, recent developments in next-generation sequencing technology offer prompt high-throughput full-length sequencing of genomic fragments of interest. This allows the identification of the whole spectrum of mutations in a gene, including any novel ones. We report two A-T families with affected children and current pregnancies. Both families are consanguineous and originate from Caucasian regions of Russia and Azerbaijan. Before our study, no ATM mutations had been identified in the older children of these families. We used ion semiconductor sequencing and an Ion AmpliSeq ™ Inherited Disease Panel to perform complete ATM gene sequencing in a single member of each family. Then we compared the experimentally determined genotype with the affected/normal phenotype distribution in the whole family to provide unambiguous evidence of pathogenic mutations responsible for A-T. A single novel SNP was allocated to each family. In the first case, we found a mononucleotide deletion, and in the second, a mononucleotide insertion. Both mutations lead to truncation of the ATM protein product. Identification of the pathogenic mutation in each family was performed in a timely fashion, allowing the fetuses to be tested and diagnosed. The parents chose to continue with both pregnancies as both fetuses had a healthy genotype and thus were not at risk of A-T.

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Keywords

Ataxia-telangiectasia, ATM gene, IDP, Louis-Bar syndrome, Prenatal diagnostic

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