ATM Gene Mutations Result in Both Recessive and Dominant Expression Phenotypes of Genes and MicroRNAs

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When the manuscript was originally published in the August 2008 issue, common microRNA nomenclature synonyms were removed to conform to journal style. Unfortunately, this rendered the manuscript difficult to find in PubMed. The abstract is being republished here with the common synonyms added to ensure efficient retrieval from PubMed:

The defining characteristic of recessive disorders is the absence of disease in heterozygous carriers of the mutant alleles. However, it has been recognized that recessive carriers may differ from noncarriers in some phenotypes. Here, we studied ataxia telangiectasia (AT), a classical recessive disorder caused by mutations in the ataxia telangiectasia mutated (*ATM*) gene. We compared the gene and microRNA expression phenotypes of noncarriers, AT carriers who have one copy of the *ATM* mutations, and AT patients with two copies of *ATM* mutations. We found that some phenotypes are more similar between noncarriers and AT carriers compared to AT patients, as expected for a recessive disorder. However, for some expression phenotypes, AT carriers are more similar to the patients than to the noncarriers. Analysis of one of these expression phenotypes, *TNFSF4* level, allowed us to uncover a regulatory pathway where ATM regulates *TNFSF4* expression through *MIRN125B* **(also known as *miR-125b* or *miR125b*)**. In AT carriers and AT patients, this pathway is disrupted. As a result, the level of *MIRN125B* is lower and the level of its target gene, *TNFSF4*, is higher than in noncarriers. A decreased level of *MIRN125B* is associated with breast cancer, and an elevated level of *TNFSF4* is associated with atherosclerosis. Thus, our findings provide a mechanistic suggestion for the increased risk of breast cancer and heart disease in AT carriers. By integrating molecular and computational analyses of gene and microRNA expression, we show the complex consequences of a human gene mutation.

The journal regrets this error.

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