Human syndromes with genomic instability and multiprotein machines that repair DNA double-strand breaks

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The present report deals with the functional relationships among protein complexes which, when mutated, are responsible for four human syndromes displaying cancer proneness, and whose cells are deficient in DNA double-strand break (DSB) repair. In some of them, the cells are also unable to activate the proper checkpoint, while in the others an unduly override of the checkpoint-induced arrest occurs. As a consequence, all these patients display genome instability. In ataxia-telangiectasia, the mutated protein (ATM) is a kinase, which acts as a transducer of DNA damage signalling. The defective protein in the ataxia-telangiectasia-like disorder is a DNase (the Mre11 nuclease) that in vivo produces single-strand tails at both sides of DSBs. Mre11 is always present with the Rad50 ATPase in a protein machine: the nuclease complex. In mammals, this complex also contains nibrin, the protein mutated in the Nijmegen syndrome. Nibrin confers new abilities to the nuclease complex, and can also bi