

Identification of the Fanconi Anemia Complementation Group I Gene, FANCI

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Objective: To identify the gene underlying Fanconi anemia (FA) complementation group I.

Methods: Informative FA-I families were studied by a genome-wide linkage analysis, which resulted in 4 candidate gene regions (39.4 Mb of genomic DNA). All (known and novel) genes in these regions were analyzed by bioinformatics and data mining for their resemblance to other FA genes/proteins acting in the FA pathway. Novel genes were selected on the basis of 1) degree of evolutionary conservation, 2) presence of nuclear localization signals and 3) pattern of tissue-dependent expression and other features. In total, 8 genes were sequenced, followed by Western analysis, siRNA knock-down and analysis of a revertant I cell line.

Results: We found a candidate, KIAA1794 on chromosome 15q25-26, to be mutated in 8 affected individuals previously assigned to complementation group I by cell fusion experiments. Western blotting indicated that functionally active KIAA1794 protein is lacking in FA-I lymphoblasts. Knock-down of KIAA1794 expression by siRNA in HeLa cells caused excessive chromosomal breakage induced by mitomycin C, a hallmark of FA cells. Furthermore, phenotypic reversion of a patient-derived cell line was associated with a secondary genetic alteration at the KIAA1794 locus.

Conclusions: First, KIAA1794 is a FA gene. Second, this gene is identical to FANCI, since the patient cell lines found mutated in this study included the reference cell line, EUFA592.

Translational Applicability: The identification of FANCI directly aids the diagnostics and counseling of individuals with suspected FA.