Discovery of a novel Fanconi anemia gene responsible of three Genome Instability Disorders

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Fanconi anemia (FA) is a rare chromosome fragility syndrome that uncovered a novel repair mechanism against DNA interstrand cross-links. Fifteen FA genes have been identified but the genetic basis in some FA patients still remains unresolved. Whole exome sequencing was used to identify two unclassified FA patients with biallelic mutations in *XPF*, a nuclease previously connected to xeroderma pigmentosum and segmental XFE progeria. Further genetic, biochemical and functional analysis suggest that the newly identified *XPF* mutations specifically disrupt the function of XPF in interstrand-cross link repair without severely compromising nucleotide excision repair. Our data show that depending on the type of *XPF* mutation patients present with three clinically distinct genome instability disorders, highlighting the multifunctional nature of the XPF protein.