

A 9 Base Pair Intron Deletion in the Human XPC DNA Repair Gene Impairs Lariat Loop Formation and Causes Exon Skipping and Multiple Skin Cancers in XP-C Patients

Sikandar Khan¹, Kyu-Seon Oh¹, Hiroki Inui¹, Steffen Emmert¹, Deborah Tamura¹, John DiGiovanna¹, Tala Shahlavi¹, Carl Baker³, Juliet Aiken², Thomas Schneider², Kenneth Kraemer¹

¹NCI, Bethesda, MD, United States, ²NCI, Frederick, MD, United States, ³NIAMS Extramural Program, Bethesda, MD, United States

The lariat branch point sequence (BPS) near the 3' end of an intron is crucial for precise processing of pre-mRNA by promoting ligation of adjacent exons. We mapped a lariat BPS to the 'A' residue at the -25 position in intron 6 of the human *XPC* gene. Two related xeroderma pigmentosum (XP) patients, XP14BE and XP377BE, had multiple skin cancers. Intron 6 of the *XPC* gene in their cells had a 9 base pair deletion (-13 to -21) that lies 3 bases downstream of the -25 'A' residue of BPS. This change abolished lariat loop formation. The deletion moved the BPS closer to the 3' end of the intron and reduced the information content of the splice acceptor from 12.3 to 6.2 bits. Their cells had no detectable normal full-length *XPC* message but expressed *XPC* mRNA with an in-frame deletion of the 90 base pair of exon 7. The cells had reduced amounts of mutant XPC protein. This mutation abolished DNA repair activity since an expression vector containing *XPC* cDNA devoid of exon 7 failed to correct the DNA repair defect in XP-C cells in a post-UV host cell reactivation assay. The mutant XPC protein did not localize to UV-induced DNA lesions in the patient's cells. Thus, the 30 amino acid sequence derived from exon 7 of the *XPC* gene is an important motif for localization to the site of damaged DNA. Abolishing lariat loop formation severely compromises XPC protein function, resulting in multiple sunlight-induced skin cancers in XP patients.