Multiple Skin Cancers in Adults with Mutations in the XP-E (DDB2) DNA Repair Gene

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TO THE EDITOR

Xeroderma pigmentosum complementation group E (XP-E) patients exhibit sunlight-induced lentiginous pigmentation without blistering on minimal sun exposure, yet they are prone to develop multiple skin cancers. Only eight XP-E patients have been reported (Bootsma et al., 1970; De Weerd-Kastelein et al., 1974; Kraemer et al., 1975; Nichols et al., 1996; Rapic et al., 1998; Itoh et al., 1999, 2000; Rapic-Otrin et al., 2003) with mutations in the DDB2 gene (Tang and Chu, 2002; Itoh, 2006), resulting in the loss of UV-damaged DNA-binding protein (UV-DDB) activity (Nichols et al., 2000; Rapic-Otrin et al., 2003) (Table 1). UV-DDB is a heterodimer of DDB1 (p127) and DDB2 (p48) (Keeney et al., 1994; Kazantsev et al., 1996) that binds with high affinity to DNA damaged by UV and is involved in initiation of global genome nucleotide excision repair (GG-NER) (Sugasawa, 2010).

We identified four adult XP-E patients from three kindreds with large numbers of skin cancers (Table 1). Patients’ written, informed consent was obtained. The Declaration of Helsinki guidelines were followed and all necessary institutional approvals were obtained. Patient XP1GO, 45 years old, in family A from Germany never experienced a blistering sunburn (Figure 1a). Diagnosed with XP at age 22, he works as a train conductor. His first tumor was removed at age 12. He had >400 basal cell carcinomas (BCCs) and squamous cell carcinoma (SCCs) and 6 melanomas treated by age 30, and now he develops ~20 skin cancers per year. He has no neurological abnormalities. Patient XP37BE is a 45-year-old Caucasian female of Dutch ancestry in family B living in the western United States (Figure 1b). She denies ever having a blistering sunburn. She developed a keratoacanthoma on her face at 7 years and was diagnosed with XP. XP37BE has had >300 BCC and SCC skin cancers but no melanomas. She has no neurological abnormalities. Patient XP66BE is a 43-year-old brother of XP37BE. He was diagnosed with XP at age 4 at the same time his older sister was diagnosed and exhibits similar clinical symptoms, yet, milder because of improved sun protection. Patient XP408BE is a 53-year-old Caucasian female in family C from the eastern United States (Figure 1c). She had no sunburns and tanned easily, but did experience significant photophobia. At age 14, she was found to have multiple skin cancers (BCCs and SCCs) on her face and a diagnosis of XP was made. She has no XP neurological abnormalities.

All cells were either established at the Human Genetic Mutant Cell Repository, the NCI Repository, or in the Department of Dermatology, Goettingen, Germany. Plasmid host cell reactivation assay was performed for cellular DNA repair capacity measurement (Emmert et al., 2000). The cells were transfected with a UV-treated plasmid containing a reporter (luciferase) gene (pCMVLuc). Compared with normal and XP variant cells, XP1GO, XP37BE, XP66BE, and XP408BE/GM01389 cells had a reduced level of luciferase expression whereas severe XP-B control cells had an even lower level (data not shown). To determine the complementation group we co-transfected the UV-irradiated pCMVLuc with plasmids that carry cloned wild-type XP complementary DNA (cDNA). Only co-transfection of the DDB2 cDNA resulted in markedly enhanced reporter gene activities (data not shown).

Abbreviations: BCC, basal cell carcinoma; cDNA, complementary DNA; GG-NER, global genome nucleotide excision repair; SCC, squamous cell carcinoma; SNP, single-nucleotide polymorphism STR, short tandem repeat; UV-DDB, UV-damaged DNA-binding protein; XP-E, xeroderma pigmentosum complementation group E.
Sequence analysis (NC_000011.8 for genomic sequence, NM_000107.1 for cDNA, and NP_000098.1 for protein) revealed a, to our knowledge previously unreported, homozygous C-to-A transversion (c.914 C > A) in exon 7 in the DDB2 gene of XP1GO. This missense mutation resulted in a p.Thr305Asn substitution (Table 1). His parents and brother were heterozygous for this mutation. The restriction enzyme BtgI cuts the normal but not the mutant sequence.

XP37BE and XP66BE showed homozygous G-to-A transitions in exon 6 of DDB2. This missense mutation (c.818 G > A) resulted in p.Arg273His and was also found in their mother and father but not their unaffected brother (Table 1). This mutation inactivates a HhaI restriction site. This mutation was previously reported in XP2RO and XP3RO cells from the Netherlands (Bootsma et al., 1970; De Weerd-Kastelein et al., 1974; Kraemer et al., 1975; Nichols et al., 1996).

The cells from patient XP408BE had compound heterozygous mutations in exon 8. One allele showed a T-to-C transversion (c.1049 T > C) resulting in p.Leu350Pro, and the other allele had a
three-base deletion (c.1045_1047del) resulting in p.Asn349del (Table 1). These two mutations were identical to the mutations previously reported in cell line GM01389 (Nichols et al., 2000). We measured 15 single-nucleotide polymorphisms (SNPs) in the DDB2 gene to determine the relationship between these two cell lines (XP408BE and GM01389). All 15 SNPs were identical in both cells (data not shown). CODIS DNA fingerprinting of highly polymorphic short tandem repeats (STRs) was then performed (Azari et al., 2007). All 13 CODIS core STR loci were detected and were identical in both cell lines (data not shown). Thus, the likelihood that the cells are not identical is approximately one in one billion. Indeed, the patient recalled having a skin biopsy for fibroblast culture when she was 21 years old.

Figure 1d shows the crystal structure of DDB2 stabilized by DDB1 and contacting the damaged DNA extensively (Chu and Yang, 2008; Scrima et al., 2008). The heterozygous DDB2 mutations (Leu350Pro and Asn349del) in XP408BE impair DDB1 binding (DDB1–DDB2 interface mutations). In contrast, the Arg273His mutation in XP37BE and XP66BE directly interferes with DNA binding (DNA-binding mutation). The new mutation, p.Thr305Asn in XP1GO cells, is located in the WD domain near a known Asp307Tyr mutation. This mutation has been reported to disrupt damage detection and complex formation with DDB1 (Rapic et al., 1998; Rapic-Otrin et al., 2003).

The diagnosis of XP-E can be considered in adults with freckle-like pigmentation without blistering on minimal sun exposure who have many skin cancers.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Agminated Segmental Nevi Demonstrating Intranevic Concordance of Braf Status

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TO THE EDITOR

Grouped patterns of pigmented lesions are infrequent. Here, we analyze a rare case of segmentally distributed, agminated nevi characterized by multiple densely clustered lesions that are confined to a developmental segment. In fact, most segmental nevi are not agminated (Happle, 2002) and arise because of perturbations in the proliferation, migration, and differentiation of embryological precursors, including melanocytes (Misago et al., 1991; Sun and Tsao, 2008). The unusual growth pattern suggests mosaicism, i.e., a condition whereby an organism is composed of two genetically distinct cell populations due to a post-zygotic mutation (Itin and Burger, 2009). Cutaneous mosaicism often manifests as lines of Blaschko, a checkerboard pattern, or a phylloid (leaf-like) pattern (Happle, 1993).

Recently, mutational analyses of melanocytic nevi have revealed that congenital moles, common acquired nevi, Spitz nevi, and blue nevi are associated with significant mutation rates in NRAS (Bauer et al., 2007), Braf (Pollock et al., 2003), Hras (Da Forno et al., 2009), and Gnaq (Van Raamdonk et al., 2009), respectively. These findings suggest that mutational activation of specific signaling molecules drives the formation of these nevi. We thus hypothesized that our patient’s agminated segmental nevi (ASN) resulted from a mosaic event related to one of the known RAS effectors.

The patient is a 58-year-old man who developed numerous grouped nevi on his right leg shortly after birth.

There was no other significant personal medical history or family history of melanoma or dysplastic nevus syndrome. On examination of his right thigh and calf, there was an extensive band-like cluster of >100 pigmented macules, plaques, and papules clinically consistent with junctional, compound, or intradermal nevi (Figure 1a). Background skin in the area showed no hypo- or hyperpigmentation. Over multiple visits, 11 clinically atypical nevi within the segment were removed although none had histological features of melanoma. Pathological evaluation of the biopsies largely showed intradermal nevi with congenital patterns (Figure 1b).

This genetic study was approved by the Research Ethics Board at Dalhousie University, and was conducted according to Declaration of Helsinki Principles. The patient also gave his written informed consent. We analyzed the 11

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Abbreviations: ASN, agminated segmental nevi; CFC, cardio-facio-cutaneous