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A Distinct Genotype of XP Complementation Group A: Surprisingly Mild Phenotype Highly Prevalent in Northern India/Pakistan/Afghanistan

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Xeroderma pigmentosum (XP) is a rare inherited disorder of DNA repair. Affected individuals cannot repair ultraviolet radiation (UVR)–induced DNA damage, resulting in an increased skin cancer risk (Bradford et al., 2011), severe sunburn in approximately 50% of patients (Sethi et al., 2013), and progressive neurodegeneration in approximately 30% (Kraemer et al., 1987; Totonchy et al., 2013). XP can result from defects in any of eight genes (*XPA–XPG* and *POLH*). *XPA–XPG* are involved in nucleotide excision repair (NER) of DNA damage (Cleaver et al., 2009).

Xeroderma pigmentosum complementation group A (XP-A) patients usually have a severe phenotype, with exaggerated sunburn and early onset of progressive neurodegeneration, which results in death, usually in the second or third decade (Anttinen et al., 2008). XPA protein is required for damage verification in the NER pathway. More than 20 different mutations have been identified in the *XPA* gene (States et al., 1998; Takahashi et al., 2010). Many of the reported cases come from Japan because of a founder mutation (c.390-1G>C) carried by 1% of the Japanese population (Hirai et al., 2006; Satokata et al., 1990). This mutation results in abnormal splicing of mRNA and subsequent production of truncated, nonfunctioning XPA protein and the typically severe clinical phenotype.

Although a diagnosis of XP-A has usually been associated with a poor prognosis, a number of XP-A patients undergoing long-term follow-up at the UK National XP Clinic have a surprisingly mild phenotype. To examine this finding further, a detailed genotype-phenotype study in this cohort was conducted. Neurological analysis included audiometry, nerve conduction studies, brain magnetic resonance imaging and neuropsychometric evaluations. Informed written consent was obtained from all patients. The study was performed in accordance with protocols approved by the Research Ethics Committee of Guy's and St. Thomas' Hospitals NHS Foundation Trust, London (reference 12/LO/0325).

Nineteen of 90 patients being studied at the UK National XP clinic were assigned to complementation group A (Table 1). Twelve of these patients, from eight consanguineous families, displayed a mild XP-A phenotype with no ocular surface disease, delayed onset or lack of skin cancer, and normal neurological and neuropsychometric evaluations (Figure 1a–h). Mean age at assessment was 32 years (range 6–79 years) and mean age at clinical diagnosis was 26 years (range 4–46 years), significantly higher than in the more severely affected XP-A group of patients, who showed progressive neurodegeneration presenting as developmental delay and cognitive impairment, sensorineural hearing loss, microcephaly, neuropathy, and cerebellar signs (Table 1). Remarkably, one of the patients, XP1CB, is aged 79 years without any XP-related neurological problems. He spent the first 30 years of his life in India working mostly outdoors and was only diagnosed clinically at age 46 years. These 12 patients all were homozygous for the mutation c.555+8A>G, which previously was reported by Sidwell et al. (2006) in a 61-year-old Punjabi woman with no neurological problems. All 12 patients included in this study, as well as the case described by Sidwell et al., originate from a 950-km stretch of land

Abbreviations: NER, nucleotide excision repair; UVR, ultraviolet radiation; XP, xeroderma pigmentosum; XP-A, xeroderma pigmentosum complementation group A

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Table 1. Summary of clinical features in the XP-A patient cohort

XP number	Age (sex)	Country of origin	Age at clinical diagnosis	Cutaneous features	SSS	Developmental/ neuropsychometric, and neurological evaluation	Age at first mucocutaneous cancer (type)	Mutation in *XPA* gene
XP9BI	6 (F)	Pakistan	6	Lentigines	0	Normal		c.555+8A>G
XP103BR	7 (F)	Pakistan	4	Lentigines	0	Normal		c.555+8A>G
XP53BR	18 (M)	Pakistan	7	Lentigines/photosensitivity	1	Normal		c.555+8A>G
XP121BR	25 (F)	Pakistan	25	Lentigines	1	Normal		c.555+8A>G
XP116BR	31 (M)	India	31	Lentigines	1	Normal	31 (BCC)	c.555+8A>G
XP2PR	32 (F)	Pakistan	32	Lentigines	1	Normal		c.555+8A>G
XP89BR-S	34 (M)	Pakistan	33	Lentigines	2	Normal		c.555+8A>G
XP1PR	35 (M)	Pakistan	35	Lentigines	2	Normal		c.555+8A>G
XP88BR	36 (M)	Pakistan	31	Lentigines	3	Normal		c.555+8A>G
XP49BR	38 (M)	Afghanistan	24	Lentigines/photosensitivity	1	Normal		c.555+8A>G
XP89BR	43 (F)	Pakistan	39	Photosensitivity	3	Normal		c.555+8A>G
XP1CB	79 (M)	India	46	Lentigines	0	Normal	46 (MM)	c.555+8A>G
XP111BR	7 (F)	Bangladesh	5	Lentigines	3	Abnormal		c.253C>T p.(Gln85TER)
XP57BR	14 (F)	Bangladesh	1	Photosensitivity	1	Abnormal		c.640dupA p.(Met214fs)
XP80BR	14 (F)	Somalia	8	Photosensitivity	3	Abnormal		c.314G>A p.(Cys105Tyr)
XP81BR	18 (M)	Somalia	12	Photosensitivity	1	Abnormal		c.314G>A p.(Cys105Tyr)
XP15BR	22 (M)	UK	0.5	Photosensitivity	3	Abnormal		c.266_267dupAA p.(Val90fs)
XP114BR	24 (M)	Pakistan	22	Photosensitivity	3	Abnormal	22 (SCC)	c.682C>T p.(Arg228TER)
XP20BR	32 (M)	Pakistan	13	Photosensitivity	3	Abnormal	22 (ocular CIN3)	c.682C>T p.(Arg228TER)

Abbreviations: BCC, basal cell carcinoma; CIN, conjunctival intraepithelial neoplasia; F, female; M, male; MM, malignant melanoma; SCC, squamous cell carcinoma; SSS, sunburn severity score (Sethi et al.,2013); XP, xeroderma pigmentosum; XP-A, xeroderma pigmentosum complementation group A.

around the Northern India/Pakistan/Afghanistan borders (Figure 1i), suggesting a founder effect present in this population.

The c.555+8A>G mutation at the eighth nucleotide of intron 4 generates a new splice donor site and results in aberrant splicing of intron 4 and nonfunctional, truncated XPA protein. However, there is a small amount of normally spliced mRNA (Sidwell et al., 2006), which results in production of residual normal XPA protein detectable in immunoblots (Figure 1j). Comparison of the upper XPA band in lanes 9–12 with the calibration in lanes 1–6 suggests that 50-μg extract from the mild XP-A cells has the same amount of (or less) XPA protein as 2.5-μg normal extract (lane 2), indicating the presence of <5% of the normal level of XPA protein in the mild XP-A cells. In contrast, no protein is detectable in the XP-A null cell line XP15BR (lanes 1 and 13). This residual protein carries out NER, consistent with the 5–15% of normal unscheduled DNA synthesis found in these patients (Figure 1k). This most likely explains their normal neurological phenotype. It has been shown that low levels of XPA protein, transfected into XPA-deficient cells, are able to significantly protect against DNA damage (Muotri et al., 2002).

Interestingly, the sunburn reactions in this group are variable, even though all patients are of similar ethnicity. This may be explained by the fact that the very small amount of functioning XPA protein may not be sufficient to repair the high level of photoproduct accumulation after sun exposure, resulting in moderate sunburn severity. However, endogenous neurological damage is likely to be generated continually at a low rate so that the low level of functioning XPA protein may be sufficient to repair the damage as it occurs, resulting in a normal neurological phenotype.

A handful of other XP-A patients with mild phenotype have been reported in the literature, although none as mild as our cohort. Four middle-aged Japanese XP-A patients presented with late-onset neurological impairment and moderate sunburn reactions, without development of skin cancer (Takahashi et al.,