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Ancient origin of a Japanese xeroderma pigmentosum founder mutation

Kyoko Imoto, M.D., Ph.D.[1,2], **Carine Nadem, B.S.**[1], **Shin-Ichi Moriwaki, M.D., Ph.D.**[3], **Chikako Nishigori, M.D., Ph.D.**[4], **Kyu-Seon Oh, Ph.D.**[1], **Sikandar G. Khan, Ph.D.**[1], **Alisa M. Goldstein, Ph.D.**[5], and **Kenneth H. Kraemer, M.D.**[1]

[1]Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[2]Department of Dermatology, Nara Medical University, Nara, Japan

[3]Department of Dermatology, Osaka Medical College, Osaka, Japan

[4]Division of Dermatology, Graduate School of Medicine, Kobe University, Kobe, Japan

[5]Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

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Xeroderma pigmentosum (XP (MIM278700)) is a rare autosomal recessive disorder [1–3]. XP patients have sun sensitivity, a 10,000-fold increased risk of skin cancer and defective DNA repair [4]. The frequency of XP in Japan is about 1:22,000 [5;6], which is much more common than in the US and Europe (about 1 per million) [2;6]. There are 8 XP DNA repair genes (*XPA* to *XPG* and XP variant).

The *XPA* gene is the predominant XP gene in Japan and is defective in about 55% of Japanese XP patients [3]. These Japanese XP patients have a severe form of XP with progressive neurological degeneration [7]. *XPA* is located on chromosome 9q22.3 and codes for a 273 amino acid protein that is involved in nucleotide excision repair [8]. More than 90% of the mutant alleles in Japanese XP-A patients have the same G to C base change mutation [7–9]. This founder mutation at the 3′ splice acceptor site of intron 3 (IVS3-1G>C) results in no detectable protein production and markedly reduced DNA repair. Approximately 1% of the Japanese general population are heterozygous carriers of this mutation [5].

In order to estimate the age of the most recent common ancestor of this founder mutation in Japan, we used haplotype analysis. We studied DNA samples from XP-A patients who were

Contact: Kenneth H. Kraemer, M.D., Chief, DNA Repair Section, Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, Building 37 Room 4002 MSC 4258, Bethesda, MD 20892 -4258, USA, 301-496-9033 FAX: 301-594-3409 kraemerk@nih.gov.

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homozygous for the founder mutation. Using Sanger sequencing, initially we measured 70 single nucleotide polymorphisms (SNP's) that were located up to 2.5 MB upstream and 2.5 MB downstream of the mutation on chromosome 9 (Table 1) as indicated on the HapMap http://www.hapmap.org. We then selected SNP's that were highly polymorphic in the Japanese population as indicated by the Japanese HapMap subjects.

To estimate the age of the most recent common ancestor of the *XPA* Japanese founder mutation, we used a likelihood-based method [10] that uses multilocus marker data. This method uses multilocus marker data to estimate the age of the most recent common ancestor of the mutation from a small number of patients. This method was originally tested through simulations and shown to be well suited to estimating the age of rare mutations. The basic assumption for the method is that the N affected individuals, all carrying the same mutation at disease locus D, descend from a common ancestor who introduced the mutation n_{gen} generations ago. The likelihood was written as a function of the recombination fraction (θ) between D and each marker, n_{gen}, and the mutation rate and allele frequencies at each marker locus. Twenty-five HapMap-based SNPs flanking D were genotyped for this analysis. Japanese HapMap subjectsa llele frequencies for these SNPs were between 50:50and 71.6:28.4. Since SNPs have a very low mutation rate, the mutation rate was fixed to 0 for this analysis. The closest short tandem repeat markers flanking D had a θ/Mb ratio of approximately 1, thus physical distance (Mb) between each marker and D was converted to θ using this ratio. n_{gen} was estimated from the size of the haplotype shared by the N affected individuals on each side of D and 95% confidence intervals were computed.

We received de-identified samples from XP-A patients in 39 Japanese families located throughout Japan except for the northern areas of Tohoku and Hokkaido. At NIH, DNA was extracted from 43 XP-A patients in the 39 families. Forty one XP-A patients in 37 of the families were confirmed to be homozygous for the *XPA* founder mutation (red column) (Table 1). DNA from 2 XP patients was found to be heterozygous for this splice mutation as well as heterozygous for nearby SNP loci and was not included in the analysis (data not shown). There were 3 affected siblings in one family (family 1) and 2 affected siblings in two other families (families 18 and 28) (Table 1 – first column, blue shading). Six of the families (families 32–37) had a history of consanguinity (4 were first cousins, 1 was second cousins and 1 unspecified) (Table 1 – first column, yellow shading). DNA was tested for 25 SNPs on chromosome 9 in the region of the *XPA* gene (Table 1 and data not shown). In families 1, 10 and 28 we tested DNA from multiple affected siblings. The siblings in each family had the same haplotypes.

We found a small region of SNP homozygosity in all the XP patients extending about 150 kb upstream and 50 kb downstream from the mutation (bright green area). The size of this region is a reflection of the relationship among the patients: a large region indicates a close relationship and a small region indicates a more ancient relationship. Using the method described above, we determined the age of the most recent common ancestor of the *XPA* founder mutation to be 120 generations (95% CI, 71–205 generations). Assuming a 20-year generation interval this corresponds to 2400 years (95% CI, 1420–4100 years) or 3600 years (95% CI, 2130– 6150 years) based on a generation length of 30 years.

The Japanese archipelago was completely separated from the Eurasian continent about 12,000 years ago. Thus this mutation occurred after this separation occurred and spread throughout the isolated Japanese population. XP is recessive and the carriers of this XPA founder mutation do not have overt clinical symptoms. All of the XP-A patients we studied were homozygous for the founder mutation indicating that both parents had the same mutation. However, only 6 of the families were aware of a close relationship between the parents of the affected XP patients. This study indicates that the common ancestor of the

other 31 families could have occurred thousands of years ago. Since this mutation is present in about 1 million Japanese carriers [5], genetic counseling for this ancient founder mutation may be considered in the Japanese population.

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Table 1

Haplotype analysis of region surrounding Japanese *XPA* founder mutation on chromosome 9q22.3

SNP ID number	rs1381532	rs2045732	rs4742692	rs3214069	rs4129746	rs7024465	rs4743102	rs953417	rs10739432	rs2149987	rs10759781	rs12380094	rs2026132	rs7853179	rs2805837	rs3176757	rs3176689	ALWN1 EXON 4	rs2808668	rs2808677	rs2808689	rs2036958	rs2808701	rs2805838	rs10818021	rs10818023
Japanese Hapmap Allele Frequency	C:52.3 T:47.7	T:48.9 C:51.1	A:47.7 G:52.3	A:84.1 G:15.9	C:53.4 T:46.6	C:51.2 T:48.8	T:52.3 G:47.7	T:48.9 C:51.1	C:43.2 T:56.8	C:42.0 T:58.0	G:50.0 A:50.0	G:53.4 C:46.6	C:46.6 T:53.4	C:47.7 T:52.3	C:46.6 T:53.4	C:81.8 T:18.2	A:53.4 T:46.6		T:53.4 C:46.6	C:53.4 T:46.6	A:54.5 G:45.5	A:69.3 G:30.7	C:60.2 T:39.8	A:25.0 C:75.0	C:35.2 T:64.8	G:71.6 A:28.4
HapMap (bp)	95,570,618	95,574,244	95,579,411	95,581,198	95,587,890	95,595,293	95,614,239	95,662,151	95,669,447	95,676,057	95,704,492	95,729,609	95,795,678	95,810,760	95,813,071	95,816,896	95,827,634	XPA G>C	95,832,273	95,853,249	95,868,270	95,876,815	95,886,046	95,886,997	95,892,258	95,894,757
Distance from XPA mutation (bp)	258,764	255,138	249,971	248,184	241,492	234,089	215,143	167,231	159,935	153,325	124,890	99,773	33,704	18,622	16,311	12,486	1,748	0	−2,891	−23,867	−38,888	−47,433	−56,664	−57,615	−62,876	−65,375
FAMILY NUMBER-SIB																										
1-A	C/T	C/T	A/G	A	C	C	T	C	C/T	C/T	G	G	C	T	C	T	A	C	Did not work	C	A	A	C	C/A	C/T	A/G
1-B			A/G	A				C	C/T	C/T								C					C	C/A		
1-C			A/G	A				C	C/T	C/T								C					C	C/A		
2	C/T	C/T	A/G	A	C	C	T	C	C/T	C/T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
3	T	T	A	A	C	No DNA	No DNA	No DNA	No DNA	No DNA	G	G	No DNA	T	C	T	A	C	C	C	A	A	C/T	C/A	C/T	A/G
4	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C/A	C/T	A/G
5	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C/A	C/T	A/G
6	C	C	G	A	C	C	T	C	C	C	G	G	C	T	C	T	A	C	C	Did not work	A	A	C	C	T	G
7	C/T	C/T	A/G	A	C	No DNA	No DNA	No DNA	No DNA	No DNA	G	G	No DNA	T	C	T	A	C	C	C	A	No DNA	C	C	T	G
8			No DNA	No DNA			T	No DNA	No DNA	No DNA	G							C					C	C/A		
9	T	T	A	A	C	C	T				G	G	C	C	C	T	A	C	C	C	A	A	C	C/A	C/T	A/G
10	C/T	C/T	A/G	A	C/T	C/T	G/T	C/T	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
11	C	C	G	A	T	T	G				G	G	No DNA	T	C	T	A	C	C	C	A	A	C	C	T	G
12	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
13	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
14	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
15	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
16	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
17	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
18-A	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
18-B			A	A				C	T	T								C					C	C		
19	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
20	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
21	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
22	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
23	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
24	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
25	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
26	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
27	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
28-A	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
28-B			A	A				C	T	T								C					C	C		
29	T	T	A	A	C	C	T				G	G	No DNA	T	C	T	A	C	C	C	A	A	C	C	T	G

SNP ID number	rs1381532	rs2045732	rs4742692	rs3214069	rs4129746	rs7024465	rs4743102	rs953417	rs10739432	rs2149987	rs10759781	rs12380094	rs2026132	rs7853179	rs2805837	rs3176757	rs3176689	ALWN1 EXON 4	rs2808668	rs2808677	rs2808689	rs2036958	rs2808701	rs2805838	rs10818021	rs10818023
30	T	T	A	A	C	No DNA	No DNA				No DNA	G	No DNA	T	No DNA	T	A	C	C	C	A	No DNA	C	C	T	No DNA
31	T	T	A	A	C	C	T	C	T	T	Did not Work	G	C	T	C	T	A	C	C	C	A	A	C	C	Did not Work	G
32	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
33	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
34	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
35	T	T	A	A	C	C	T				G	G	No DNA	T	C	T	A	C	C	C	A	A	C	C	T	G
36	T	T	A	A	C	C	T	C	T	T	G	G	C	T	C	T	A	C	C	C	A	A	C	C	T	G
37	T	T	A	A	C	No DNA	No DNA				No DNA	G	No DNA	T	No DNA	T	A	C	C	C	A	No DNA	C	C	T	No DNA