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Founder Mutations in Xeroderma Pigmentosum

Deborah Tamura[1], **John J. DiGiovanna**[1,2], and **Kenneth H. Kraemer**[1]

[1]Dermatology Branch, National Cancer Institute, Bethesda, Maryland, USA

[2]Division of Dermatopharmacology, Department of Dermatology, The Warren Alpert School of Medicine at Brown University, Providence, Rhode Island, USA

Abstract

In this issue, Soufir *et al.* report a founder mutation in the *XPC* DNA repair gene in 74% of families with xeroderma pigmentosum (XP) in the Maghreb region (Algeria, Morocco, and Tunisia) of northern Africa. These patients have a high frequency of skin cancer. The presence of this founder mutation provides an opportunity for genetic counseling and early diagnosis of XP.

Genetics of xeroderma pigmentosum

Xeroderma pigmentosum (XP) is a rare autosomal recessive genodermatosis with a markedly elevated risk of developing sunlight-induced cancers of the skin and eyes (Kraemer *et al.,* 2007). XP is caused by mutations in DNA repair genes that protect cells from UV-induced DNA damage. There are seven XP complementation groups (XP-A to XP-G) representing nucleotide excision repair genes that are mutated in patients with X P. An additional “variant” form (XPV) has a defect in polymerase eta that bypasses DNA photoproducts (Kraemer *et al.,* 2007).

XP is found in all races and throughout the world, with a frequency that ranges from about 1 per million in Europe and the United States (Kleijer *et al.,* 2008) to 1 per 22,000 in Japan (Hirai *et al.,* 2006). In this issue, Soufir *et al.* (2010) report a large genetic analysis of 86 patients with XP in 66 unrelated families from the Maghreb region (Algeria, Morocco, and Tunisia) of North Africa. They reported that 85% of families had mutations in the *XPC* gene and 12% had mutations in the *XPA* gene. Importantly, 74% of families had the same homozygous two-base deletion (c.1643_1644delTG) in the *XPC* gene that leads to premature termination of the XPC protein. This is in accord with reports from the same region of this homozygous mutation in 100% of 14 XP families from different parts of Tunisia (Ben *et al.,* 2009), in two other African patients with XP (Khan *et al.,* 2006), and in a Sudanese XP family (Mahindra *et al.,* 2008).

Mutation hotspot or founder mutation?

Why was the same mutation present in so many patients? In theory, the mutations could have arisen independently. The localized DNA sequence in the *XPC* gene might be genetically unstable and produce a mutation “hotspot” (Figure 1a and Table 1). Indeed, a mutation hotspot is present in the *XPD* gene. Mutations leading to p.R683W are present in unrelated patients with XP from many parts of the world (Lehmann, 2001).

Correspondence: Kenneth H. Kraemer, Dermatology Branch, National Cancer Institute, Building 37 Room 4002, MSC 4258, Bethesda, Maryland 20892, USA. kraemerk@nih.gov.

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An alternative explanation is that the African patients with XP had a common ancestor who carried this mutation— a "founder" mutation. In this case the two-base deletion mutation (delTG) in the *XPC* gene might have arisen spontaneously in one allele in an individual many generations ago (Figure 1b). Because the other allele is normal, this person would have been a normal-appearing heterozygous carrier. Social customs in some parts of the world encourage marriage within the local community or among cousins. Similarly, geographic isolation, such as living on an island (as in Japan) or in an isolated area (the Maghreb region is bounded by the Sahara Desert, the Atlas Mountains, and the Mediterranean Sea) would promote intermarriage. These factors could eventually produce individuals with the same mutation in both alleles, i.e., individuals with clinical XP with a homozygous two-base deletion, as seen in most of the African patients with XPC reported by Soufir *et al.* (2010). The DNA surrounding the mutation (the haplotype or pattern of single-nucleotide polymorphisms (SNPs) or microsatellites) would also have been passed from generation to generation. Thus, individuals with a founder mutation would share the same haplotype (Figure 1b and Table 1). In contrast, individuals with hotspot mutations would have different haplotypes (Figure 1a).

XP founder mutations

The observation that most North African patients with XP in a single geographic area have the same mutation suggests the presence of a founder mutation. Finding that they share the same haplotype would provide direct evidence of a common ancestor. The size of the common haplotype region of the chromosome can be related to the number of generations that link the patients to their "most recent common ancestor." A large region of haplotype commonality suggests a recent ancestor. Changes in DNA, such as chromosome crossing over during multiple generations, may result in reductions in the size of the common region. Thus, smaller regions of identical haplotype suggest a more distant ancestor. Soufir *et al.* (2010) used this elegant technique to show that the most recent common ancestor of the Maghrebi patients with XPC with delTG lived about 50 generations ago. If a generation is 25 years, then this XPC founder mutation arose in the Maghreb region about 1,250 years ago. Similarly, a founder mutation in the *XPA* gene of Japanese patients with XP was described as arising about 120 generations (or about 2,400 years) ago (Imoto *et al.,* 2008).

Carriers of XP founder mutations in the general population

The frequency of the founder mutation in the population may vary. Evidence of a common ancestor was found linking XP families in Italy and Turkey with a common ancestor 300–500 years ago (Gozukara *et al.,* 2001). However, the mutation Soufir *et al.* (2010) found in the *XPC* gene (c.1840C>T) was identified in only two families. On the other hand, the *XPA* founder mutation in Japan was estimated to be present in 1% of the general population, or about 1 million people (Hirai *et al.*, 2006). Four other founder mutations were reported in Japanese patients with variant XP (Masaki *et al.,* 2008). An *XPD* founder mutation was also reported in Kurdish Iraqi Jews in Israel, but the population frequency is not known. The finding of the homozygous *XPC* delTG founder mutation in many families in North Africa suggests that it is not rare. For recessive disorders, normal-appearing heterozygous carriers are much more common than homo zygotes in the general population. A survey of the Maghreb population for the frequency of this founder mutation should be performed.

High frequency of a founder mutation for a serious disease in the general population could have an impact on medical care and genetic counseling. In the United States, genetic screening is performed on newborns for diseases that meet several criteria: it can be identified at a time (24–48 hours after birth) at which it would not ordinarily be detected clinically; a test with appropriate sensitivity and specificity is available for it; and there are

demonstrated benefits of early detection, timely intervention, and efficacy (Watson *et al.,* 2006). Neonatal testing is currently performed for several dozen genetic disorders, including phenylketonuria, cystic fibrosis, and sickle cell disease. In the United States, most of the *XPC* mutations identified to date have been found in one or a small number of families without a founder mutation (Khan *et al.*, 2006). High frequency of an XP found er mutation in other parts of the world makes genetic screening by DNA analysis feasible. Early diagnosis and institution of sun protection measures are essential for preventing skin cancer and preserving vision in patients with XP, and early detection can save lives. Thus, it is reasonable to consider newborn screening for XP in selected populations with a high frequency of a founder mutation. Similarly, premarital screening for the presence of the founder mutation may be a part of genetic counseling. The founder mutation also may be used for prenatal diagnosis in pregnancies where the parents are carriers.

Clinical phenotype of XP patients with founder mutation

Most African patients with XPC with the delTG mutation in both alleles have similar clinical features consisting of photosensitivity, pigmentary changes, and early onset of skin cancer without neurological involvement (Mahindra *et al.*, 2008; Ben *et al.*, 2009; Soufir *et al.*, 2010). However, two patients were reported to be homozygous for the delTG but with neurological involvement (Soufir *et al.*, 2010). This is similar to XP-C patients reported with homozygous mutations in the initiation codon with and without neurological involvement (Khan *et al.*, 2009). These data suggest that neurological involvement may be caused by consanguinity with homozygosity of other unknown genes or by modifying genes or prenatal exposure to teratogens or infectious agents. The data also point to possible problems in trying to predict phenotype when only the genotype is known.

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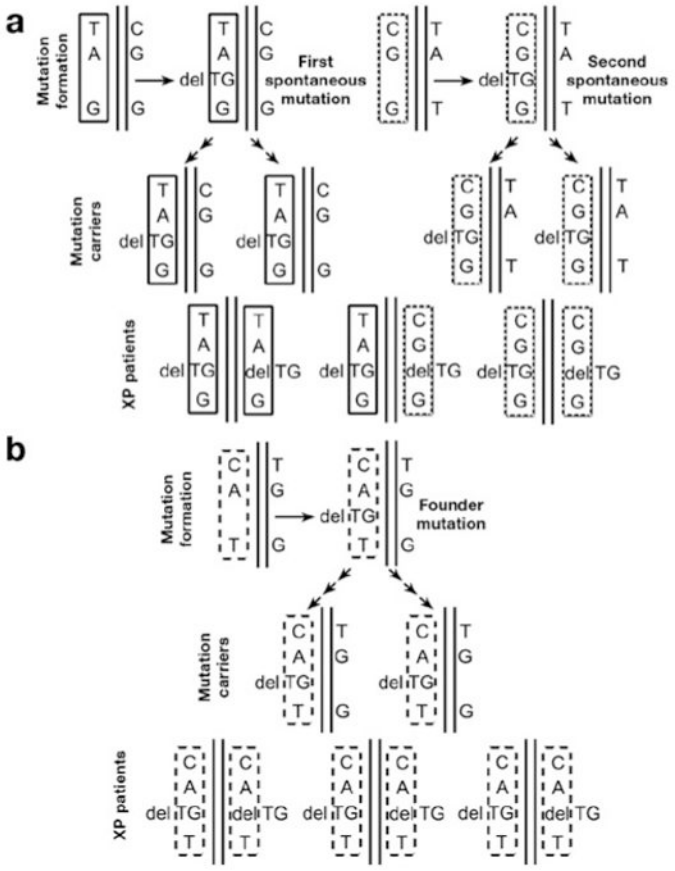

Figure 1. Haplotype analysis distinguishes a mutation hotspot from a founder mutation

(**a**) Mutation hotspot. (Top row) The same mutation (delTG) arises independently in two individuals with different single-nucleotide polymorphism (SNP) haplotypes in the region of the mutation: TA (delTG) G (solid rectangle) and CG (delTG) G (dotted rectangle). Over generations these individuals pass the delTG mutation and adjacent regions to their progeny, who are asymptomatic carriers with one mutated allele and one normal allele (center row). Eventually, carriers of the delTG mutation have children with the same mutation in both alleles (bottom row). All of these affected individuals (XP patients) are homozygous for the delTG mutation. However, different XP patients have different haplotypes (TA (delTG) G, CG (delTG) G, or both). (**b**) Founder mutation. (Top row) The delTG mutation arises in one individual with a SNP haplotype in the region of the mutation: CA (delTG) T (dashed rectangle). This individual passes the delTG mutation and adjacent regions to many generations of progeny who are asymptomatic carriers with one mutated allele and one normal allele (center row). Eventually, two carriers of the delTG mutation have a child with the same mutation in both alleles (bottom row). All of the affected individuals are homozygous for the delTG mutation and have the same haplotype (CA (delTG) T).

Table 1

Primer on founder mutations

Founder mutation	A mutation that arose in a common ancestor; the same mutation is found in related individuals who share the same haplotype; it may have arisen many generations ago; mutation carriers often live in same isolated geographic region; it can be of low or high frequency in the population
Mutation hotspot	An area within a gene that is prone to frequent spontaneous mutations such that the same mutation is found arising in unrelated individuals; often found scattered in different parts of the world; may have arisen recently; represents genetic DNA instability at the site of mutation
Public health measures	Screen for frequency of the founder mutation in the general population; newborn nursery screen if high frequency exists
Genetic counseling	Counseling of concerned individuals regarding the risks for genetic disorders; premarital founder mutation screening in members of a defined group; prenatal diagnosis may be possible in families in which both parents are carriers of the founder mutation
XP founder mutations identifed	Japan: XPA, XP variant; North Africa: XPC; Israel: XPD