Xeroderma pigmentosum in South Africa: Evidence for a prevalent founder effect

M. KGOKOLO[1], F. MORICE -PICARD[2], H.R.R. EZVANI[2,3], F. AUSTERLITZ[4], F. CARTAULT[5],

A. SARASIN[6], M. SATHEKGE[1], A. TAIEB[2,3] and C. GED[2,3,*]

[1]University of Pretoria, Private Bag X169, Pretoria, 0001 South Africa

[2]National Reference Center for Rare Skin Disorders, CHU de Bordeaux, Bordeaux, France

[3]Université de Bordeaux, INSERM, BMGIC, U1035, F-33076 Bordeaux, France

[4]Université Paris-Diderot, Musée de l'Homme, CNRS/MNHN UMR7206, F-75116 Paris, France

[5]CHU Felix Guyon, Génétique Moléculaire, Saint-Denis, F-97405 La Réunion, France

[6]Université Paris-Sud, Institut Gustave Roussy, UMR8200 CNRS, F-94805 Villejuif, France

*Correspondence: Cécile Ged. E-mail: cecile.ged@u-bordeaux.fr

Dear Editor, Xeroderma pigmentosum (XP) is a rare, autosomal, recessive disease caused by defective repair of UV-induced DNA lesions due to various genetic defects affecting genes involved in the nucleotide excision repair pathway. Seven complementation groups have been described and named XP-A to XP-G, (OMIM 278700, 610651, 278720, 278730, 278740, 278760, 278780, respectively) with an additional XP variant form (OMIM 278750) due to a defect in translesion DNA synthesis. Clinical manifestations are caused by the cutaneous and mucosal hypersensitivity to UV exposure, which induces multiple precocious cancerous lesions and premature skin ageing. XP has been described worldwide and shows the worst manifestations in sunny regions, with underdiagnosis and limited access to preventive and accurate care.[1]

In the present study, conducted by the Dermatology Department of Pretoria Hospital (South Africa), 16 unrelated families, composed of 17 affected patients, including two male twins (#SAT16 and 17), and 13 parents, originating from various provinces located in the north-east part of South Africa or neighbouring countries (Mozambique, Zimbabwe) underwent bioclinical evaluation and genetic study. The study was approved by the bioethics committee of Pretoria University, and the patients/guardians provided signed, written informed consent.

Blood samples for routine biological tests and saliva samples (Oragen-DNA Kit; DNA Genotek, Ottawa, ON, Canada) were collected in Pretoria and analysed in Bordeaux (France).

We focused first on the *XPC* gene and identified a prevalent mutation (c.2251-1G>C) already described in the Comoros, as present in the homozygous state in 12 of the 13 XP-C. The remaining patient was compound heterozygous, with the first allele being the common splicing defect and the second allele a nonsense mutant, previously described in India (Table 1).

Table 1. Phenotypic and genotypic characteristics of patients with xeroderma pigmentosum

	Families	Sex	Age of onset	Age at time of examination	Clinical profile (skin, oral cavity, eye tumours)
XPC					
	SAD03	F	18 months	19 years	BCC/SCC (16 years); cheilitis; tongue and eyelid tumours
	SAD04	F	6 months	18 years	BCC/SCC (6 years); tongue and eye tumours
	SAD06	F	9 months	10 years	BCC/SCC (6 years); cheilitis; tongue tumour; corneal scarring
	SAD08	M	2 years	6 years	BCC/SCC (2 years); tongue tumour; keratopathy
	SAD10	M	2 years	8 years	BCC/SCC (4 years); tongue tumour; corneal scarring
	SAD11	F	3 years	16 years	BCC/SCC (3 years); tongue tumour; corneal scarring
	SAD12	F	2 years	8 years	BCC/SCC (2 years); tongue, lip and eyelid tumours; keratopathy
	SAD14	M	–	3 years	Freckling on sun-exposed areas; no tumours
	SAD15	M	1 year	10 years	BCC/SCC (3 years); tongue tumour; corneal scarring
	SAT16, SAT17[a]	M	2 years	9 years	BCC/SCC (2 years); tongue tumour; keratoconjunctivitis
	SAD18	F	1 years	6 years	BCC/SCC (3 years); fibrosing keratopathy
	SAD19	F	9 months	6 years	BCC/SCC (2·5 years); lip and eyelid tumours
XPD					No skin tumours
	SAD05	M	2 years	4 years	Freckling; frequent sun burns; cheilitis; photophobia (uk[b])
	SAD09	F	14 months	10 years	Freckling; frequent sunburn; cheilitis; photophobia; MR

BCC, basal cell carcinoma; MR, mental retardation; SCC, squamous cell carcinoma.
[a]SAT16 and SAT17 are twins; [b]uk, excision of unique eye lesion of unknown origin; [c]biallelism was confirmed by parental analysis.
XPC gene analysis (NM_004628); all patients[c] except SAD11 had the same genotype: *XPC*: [c.2251-1 G>C];[c.2251-1 G>C]; genotype of SAD11 was *XPC*:[c.2251-1 G>C]; [c.1677C>A p.Tyr559ter], which represent known variants of the *XPC* gene.[6–8]
XPD gene analysis (*XPD*/*ERCC2* NM_000400): SAD05 genotype[c] XPD: [c.1777G>A p.Gly593Arg]; [c.1811T>G p.Val604Gly]; SAD09 genotypec[c]: XPD, [c.1871C>T p.Pro624Leu];[c.2047C>T p.Arg683Trp], which represent novel missense mutations in XPD not described in the gnomAD, ESP or dbSNP databases, and predicted by PolyPhen, SIFT and MutationTaster *in silico* toolsimplemented through Alamut interactive Biosoftware to be probably pathogenic or disease-causing and a frequent missense variant,[9] respectively.
The study included two unrelated patients (SAD07 and SAD13) whose genetic analysis remained inconclusive after next-generation sequencing of genes including *XPA*, *XPC*, *XPV-POLH*, *XPE-DDB2*, *DDB1*, *XPD-ERCC2*, *XPB-ERCC3*, *XPF-ERCC4*, *XPG-ERCC5*, *ERCC1*, *ERCC6*, *ERCC8*, *GTF2E2*, *GTF2H5-TTDA*, *MPLKIP-TTDN1*, *UVSSA*, *RNF113*, *DCAF17*, *ABCC6* and *ADAR*. Fifteen microsatellite markers (30·40–36·90 cM) surrounding the *XPC* locus (31·88 cM) were studied in patients with XP-C carrying the prevalent mutation in order to characterize a possible founder effect.[3]

All patients had skin types IV/V, early onset of the disease and little photoprotection. The youngest child, aged 3 years, had prominent skin changes, dyschromia, freckling and xerosis but no tumours. In other patients, multiple precocious skin tumours in sun-exposed areas, with tongue and lip involvement, were noted. Ocular lesions were prominent, as mentioned in a well-documented clinical study of patients with XP from South Africa.[2] Neurological examination was unremarkable in all patients. Fatal evolution due to XP in a sibling was reported twice (Families #SAD03 and SAD06).

Massive parallel sequencing (next-generation sequencing) was then used to analyse 20 genes potentially involved in XP or dyschromia-related disorders. Two families were diagnosed with XP-D (*ERCC2* gene) while the analysis was inconclusive in two young patients (aged 4 and 6 years), who could benefit from whole exome/genome analysis.

Patients with XP-D from two independent families (#SAD05 and SAD09) mainly experienced sunburn following minimal sun exposure, with freckling, and had not developed any tumour to date. Each patient had compound heterozygosity combining two missense mutants (Table 1). The girl (#SAD09), aged 10 years, had learning difficulties, and had a novel missense and a well-characterized deleterious variant of the *XPD* gene. The boy (#SAD05), aged 4 years, had two novel missense variants. The *XPD* gene variants were confirmed by targeted resequencing and subjected to *in silico* analysis to evaluate clinical significance. The predictive tools classified the novel variants as disease-causing with nonambiguous scores.

We estimated the time elapsed since the appearance of the common ancestor of *XPC* mutation carriers in the South African population (including Mozambique and Zimbabwe) using several microsatellite markers linked to the disease 3p25 locus.[3] The estimated per generation growth rate being 1·24 [95% confidence interval (CI) 1·22–1·38], mutation dating was evaluated as 43·3 generations (range 37·3–52·4), which translated into 1082 years (range 932–1309) assuming a generation time of 25 years. Interestingly, using the same technology, the age of the same *XPC* mutation in patients from the Comoros had been estimated to be approximately 770 years. It is plausible that this *XPC* mutation appeared in the Bantu-speaking population and travelled south along the east coast of Africa more than 1000 years ago. Heterozygous XP individuals may have lived in African east-coast countries, such as Mozambique, and moved further to South Africa more than 1000 years ago. A few centuries later, XP heterozygotes left the mainland to people Comoros, supporting the hypothesis of common ancestors.

New insights on XP distribution are gained by the means of deep genotyping as recently performed in patients from various origins.[4] If NGS technology were able to speed up the genetic diagnosis in patients with XP-D, a primary screen would remain useful to target a prevalent DNA repair gene, suspected from the knowledge of the geographical origin of patients with XP. As noted in the different countries explored so far, XP-C is the most frequent complementation group in this series, with recurrent *XPC* gene defect, as described in North Africa.[5] Moreover, our study provides insight concerning a common ancestry between South African and Comorian patients sharing the same prevalent XPC mutant.

Acknowledgments

We thank the French Patient Association (Association pour le Xeroderma Pigmentosum, 'Les Enfants de la Lune') for financial support that permitted the development of the NGS sequencing strategy, and the South Africa patient support group (XP Society) for help in identifying patients in Pretoria. Expert technical work was performed by L. Carrat (Molecular Biology Platform of Bordeaux CHU, Pellegrin Hospital). We are grateful to the Molecular Genetic Department for kind assistance with bioinformatics tools.

References

[1]Di Giovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. *J Invest Dermatol.* 2012; 132: 785– 96.

[2]Jacyk WK. Xeroderma pigmentosum in black South Africans. *Int J Dermatol.* 1999; 38: 511–914.

[3]Austerlitz F, Kalaydjieva L, Heyer E. Detecting population growth, selection and inherited fertility from haplotypic data in humans. *Genetics* 2003; 165: 1579– 986.

[4]Fassihi H, Sethi M, Fawcett H *et al*. Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect. *Proc Natl Acad Sci USA* 2016; 113: E1236– 45.

[5]Soufir N, Ged C, Bourillon A *et al*. A prevalent mutation with founder effect in xeroderma pigmentosum group C from North Africa. *J Invest Dermatol* 2010; 6: 1537– 942.

[6]Cartault F, Nava C, Malbrunot AC *et al*. Gene splicing mutation has lead to the highest worldwide prevalence of xeroderma pigmentosum in black Mahori patients. *DNA Repair* 2011; 10: 577- 585.

[7]Ijaz A, Basit S3, Gul A *et al*. XPC gene mutations in families with xeroderma pigmentosum from Pakistan; prevalent founder effect. *Congenit Anom (Kyoto)* 2019; 59: 18- 21.

[8]Tahmhankar PM, Iyer SV, Ravindran S *et al*. Clinical profile and mutation analysis of xeroderma pigmentosum in Indian patients. *Indian J Dermatol Venereol Leprol* 2015; 81: 16-22.

[9]Falik Zaccai TC, Erel-Segal R, Horev L *et al*. A novel XPD mutation in a compound heterozygote; the mutation in the second allele is present in three homozygous patients with mild sun sensitivity. *Environ Mol Mutagen* 2012; 53: 505- 14.