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### Mini-review

# Xeroderma pigmentosum family support group: Helping families and promoting clinical initiatives

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### ABSTRACT

The past two decades of research into Xeroderma pigmentosum (XP), an autosomal recessive disease, has been marked by significant progress in understanding the molecular basis of this rare disease. More importantly, especially from the perspective of the affected families, is that this knowledge has been applied to diagnose the condition both *in utero* as well as in the very early days of life. The eight known XP genes and their different phenotypes present a number of challenges that the XP Workshop sponsored by the NIH in 2010 has highlighted. There is little current treatment specifically designed for any of the XP types other than standard dermatological and neurological evaluations and care. The Xeroderma Pigmentosum Family Support Group (XPFSG) is dedicated to serving families with children and adults with all forms of XP and to help them better understand the condition, to identify practical measures which can be taken by the XP patients and their families to mitigate the effects of the disease, and to serve as patient advocates to help families discuss issues with their physicians. We summarize our efforts in terms of outreach within the US and abroad to affected families and discuss XPFSG-sponsored clinical initiatives that include molecular diagnoses, treatment, and initial proof-of-concept studies that can, if successful, improve the lives of XP patients in the near term.

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### 1. Introduction

#### 1.1. The XPFSG—what it is and what it does

“Every child deserves a day in the sun”. This is the motto for a small grass roots organization founded by Michele Milota from Sacramento, California in December 2005. XP, a rare, autosomal defect in the DNA repair system, is responsible for numerous clin-

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**Fig. 1.** Infant with XPA showing extensive skin lesions commonly associated with disease.

ical problems for patients and their families. XP prevents those afflicted by the most common forms of the disease from engaging in any activity in the sun or other sources of ultraviolet radiation (UVR). Michele, along with other families who share in the daily tribulations of this disorder, have established themselves as a round-the-clock information-friendly group of compassionate soldiers fighting for the lives of their own family members and others affected by XP.

The goal of the XPFGS is to help all individuals affected by this genetic condition. Due to the normal inclinations of all individuals to live within the socially and biologically mandated rhythms of natural light, it is a formidable task to keep XP kids from being exposed to the harmful effects of the sun (Fig. 1). This small group of highly motivated individuals is dedicated to improving the quality of life for those who suffer from XP in the form of emotional support, education, assisting that the correct diagnosis is made, effective disease management options, and ultimately, a cure. The vast number of DNA test models, charts and grim cellular findings might make the latter seem unlikely but this Group will hear none of that. “We look for a cure. . .always. . .but, if it doesn’t come, it won’t be because we didn’t give it every ounce of effort that is within us” touts Michele, the mother of a seven-year old daughter with XPC.

1.2. XPFGS and fundraising

From a fundraising perspective, XP ranks low on the numerical scale with organizations that support better known diseases like Breast Cancer, Leukemia, Muscular Dystrophy, and other such causes that regularly make the headlines. XP affects about one person in every 1.5 million people in the United States. Fundraising, and an unyielding dose of tenacity, is the primary vehicle for success for the XPFGS. Everyone affiliated with this Group is encouraged (and assisted) to engage in fundraising. For most non-profit groups, fundraising is a universally understood and accepted way to gather the money a ‘giving’ people wish to share. . .as a means to an end.

**Table 1**  
 XP individuals affiliated with the XFSG by gender, XP type and current status.

Gender	Age (as of 2010)	XP Type	Status
M	8	Unknown	Alive
F	8	C	Alive
F	15	D	Alive
F	23	A	Deceased
F	10	A	Alive
F	8	C	Alive
M	22	C	Alive
M	13	Unknown	Alive
F	7	C	Alive
F	25	G	Alive
F	12	C	Alive
M	7	C	Alive
M	16	C	Alive
F	14	C	Alive
M	NA	C	Alive
M	16	C	Alive
F	25	A	Alive
F	23	A	Alive
M	7	C	Alive
M	55	V	Alive
F	55	E	Alive
M	17	C	Alive
F	26	C	Alive
M	35	V	Alive
M	4	C	Alive
F	2	D	Alive
F	10	D	Alive
F	8	C	Alive
M	NA	C	Alive
M	NA	C	Alive
F	18	C	Alive
M	11	A	Deceased
F	16	A	Deceased
M	33	V	Alive
F	29	V	Alive
F	8	C	Alive
M	4	A	Alive
F	17	C	Alive
F	18	Unknown	Alive
M	16	C	Alive
M	16	Unknown	Alive
F	15	Unknown	Alive
F	17	D	Alive
F	16	C	Alive
F	11	C	Alive
M	5	C	Alive
F	5	C	Alive
M	8	D	Alive
F	18	Unknown	Alive
F	15	Unknown	Alive

For this Group, it is an attempt to gain recognition from a ‘largely unaware’ audience. These ‘mostly’ children with XP suffer from a variety of medical problems ranging from multiple skin cancers to neurological deficiencies and a shortened lifespan, depending on the severity of their disease and the quality of their care. Some individuals live longer, but the average XP child lives no more than three decades (median age 29 with neurodegeneration; 37 without. See Bradford P. NCI). In the past 16 months, the XPFGS has lost four XP patients, ranging in age from 15 to 32 years of age (Table 1).

1.3. XPFGS and family support

As rare as XP is, the presence of various genotypes and the challenges met by each patient ranges in appearance and severity. For all of those diagnosed with XP, there is one hurdle that is apparent from the time a child begins to explore the world outside the home. From as early as three or four years old, XP children begin to realize their unique challenges in social settings. Everything they see on television or through their UV-tinted windows is ‘fantasy’ for



Fig. 2. Young XPC patients with typical solar/UV protection gear.

them, and difficult for the parents and siblings who must struggle to maintain a sense of normalcy.

A case is used to illustrate the day-to-day issues faced by families with a XP child. A seven-year-old girl was diagnosed with XP when she was just a toddler. Her freckled face has not been touched by the sun since then. Her parents keep her busy and have labored to ensure that the changes to her environment keep her safe from UVR. She has been fitted with all of the tools necessary to protect her from skin cancers. She has an assortment of masked hats and hoods, gloves for her hands, sunscreens, sunglasses and a UV meter that alerts her when all of the above are not enough to ensure her safety from UVR (Fig. 2). The windows in her family home and in her family vehicle are covered with a UV safe tint (UV protective film provided by the 3 M Company). The school board, and a decision by the State of California to provide all children with the ability to attend school despite any disability, allows her school to be completely UV safe when she is indoors. Outside, however, is where the little girl yearns to be with her friends. The other children are sympathetic to her challenges and, on most every occasion, she is accompanied by alternating tiny volunteers to play indoors with her during recess and Phys Ed. With the help of a plethora of adult sympathizers and XPFSG volunteers, there is plenty for her to do. And, she's had quite the education with regard to XP. Yet, the windows and the sounds of the crowded playground tug at her deepest and most basic urges. . .to be one with her peers. At seven, despite the restrictions imposed on her, she is doing well. At 10 years old, then 13, the desire to be included with her peers will most likely be stronger, and the challenges to be overcome will be different. The need for children to explore their social boundaries is difficult even in families where such life-saving restrictions do not exist. Social agendas, especially outdoor ones, become more prominent as children grow. At 13, she will not be afforded the opportunity to attend afternoon pool parties, softball games, and strolls in the park with her peers. She will likely become more socially awkward and suffer a higher incidence of rejection by the boys and girls being pulled to conform within their peer group.

The XPFSG is acutely aware of these challenges and works diligently to educate families of XP children. Research, education, prevention and an ultimate solution is a daily focus for the XPFSG. There are just 250–300 cases of XP in North America, and the XPFSG has reached out to every one of them. From website to fliers to phone call, this group stays actively involved with the challenges

faced by families and patients alike. Members of this group are found across most of the United States and Canada. They have sister groups in Europe and beyond with whom they communicate on a regular basis. The XPFSG works with interested and sympathetic volunteers from a host of compassionate companies such as the 3 M Company, sunscreen manufacturers, and even individual physicians and scientists who donate their time and service to the cause.

For all XP patients, young and old, there is a spectacular event held each year, courtesy of the XPFSG and its many volunteers. That event is the XP Family Retreat (Fig. 3). Through laborious fundraising efforts and donations, all patients and their immediate families are invited to attend the retreat in an effort to share stories and experiences. For the XP child, these retreats have proven to consist of fond memories, immeasurable in terms of comfort, camaraderie and the feeling of not being alone. What parent would not want his/her child to experience the joy of playing with other children? XPFSG holds seminars for XP parents while their children are participating in a number of fun-filled activities in an indoors camp-like setting. Since XP is such a rare and isolating condition, it is important for families to meet others with XP and they often form lifelong friendships. For scientists, physicians and family members, it has become exceptionally beneficial in terms of sharing of information, updates on the basic and clinical sciences, and above all on providing hope to the families. Table 1 provides a breakdown of the XP population served by the XPFSG.

The XPFSG helps families with day-to-day UV protection. Once contacted by a family with XP, a UV protective light meter is sent to the family of the XP child. This device helps to monitor the amount of surrounding UV, giving families some sense of what level of exposure might be harmful. The XPFSG also works with 3 M to provide UV-protective film for the homes, cars, and schools of XP individuals, allowing the XP patient to be protected from the solar radiation penetrating through the windows. With the UV film the XP children are able to see outside safely. UV-protective hoods are worn by many XP patients and the XPFSG provides the materials needed to fabricate a hood. All UV protective services are provided at no cost to the XP patient and their families.

#### 1.4. Clinical intervention and research in Guatemala

The XPFSG has teamed up with Good Samaritan International of Washington, DC to send medical teams to Guatemala to help with a cluster of individuals suffering from this disease in a remote village outside of Barillas. Of the 23 cases of XP initially diagnosed there, only 11 children survive. XPFSG has been to Guatemala three times since 2007 and has actively participated in two surgical missions since (in 2009 and 2010). In a combined effort with other groups, they have produced a documentary, "Hidden From Light", featuring the XP children in this tiny isolated parish. The work of physicians, nurses and volunteers from the XPFSG and outside institutions, along with Peggy Tuttle of Good Samaritan, has focused on treating children with extensive skin cancers in this heavily afflicted mountain parish. Dr. Bari Cunningham, the XPFSG's lead international care physician and a Board-certified dermatologist, enlisted the help of other medical professionals for these medical and humanitarian missions. Likewise, Dr. Cunningham is primarily responsible for all international medical care undertaken by XPFSG.

Dr. James Cleaver at the University of California San Francisco (UCSF) Medical School evaluated biopsy and tumor samples retrieved from these patients. The isolated rural coffee farming community in Barillas, Guatemala, had a high incidence of solar-induced skin cancers resulting in premature death before children reached their teens from complications of malignancy and infections. The clinical description and village history of significant inbreeding suggested these children were cases of homozygosity



## 2008 XPFSG Retreat Sacramento, California



Fig. 3. XPFSG Retreat, Sacramento, California 2008: a place to make friends and learn about new developments in the management of XP.

for XP. The initial assessment also showed no evidence for neurological symptoms, suggesting that the likely candidate genes could be *XPC*, *XPV* or *XPE*, none of which show significant major neurological symptoms, although a late onset of neurological complications would not be seen due to the young ages and mortality rates of the children. The symptoms were, however, much more severe than usually observed in the US, presumably due to the intense sun exposures. We first carried out western analysis on lymphoid cultures [1] and immunohistochemistry on fixed tissue [2] using an antibody to XPC, and successfully detected loss of function of XPC. The lymphoid cells were very sensitive to UV damage, consistent with this loss of function [1]. Sequencing the XPC exons we identified that the Guatemalan patients were homozygous for a single base pair deletion in exon 8 of the XPC gene that resulted in a frame shift and premature termination (Exon 8, C940del-1, 969stop).

The high incidence of XP in this village is most likely due to the immigration of a single individual carrying the—C deletion that then spread through the population due to intermarriage. A similar “founder effect” or examples of common descent have been reported for XP in several other locations world-wide [3–5]. A detailed epidemiological survey of the village was deemed unjustified, in favor of continued medical intervention involving cancer surgery, skin transplantation, and education about the solar etiology of the skin disease. The isolation of this Guatemalan community and the extreme severity of the clinical symptoms present major challenges for clinical investigations and for humanitarian intervention.

The mutation is in a site of the XPC gene that is cleaved by several restriction enzymes, depending on methylation status (wild type sequence cleaved by: BssKI, StyD4N1, NciI, ScrFI. Mutated XPC cleaved by: BsrFI), so an RFLP analysis of a PCR-amplified region of about 300nt would permit diagnosis of the carriers in the village. The skin cancers were of all major kinds: actinic keratoses, squamous cell carcinomas (SCC), basal cell cancers (BCC), and melanomas. Samples of these, that were discarded tissue from the surgeries, have been returned to the UCSF, where whole exome sequencing of non-melanoma skin cancers (NMSC) is underway, having already been completed for non-XP patients and organ

transplant patients (Choi R., Cleaver J.E. unpublished data, in preparation).

## 2. XPFSG-research initiatives

Given the increased understanding of the molecular genetics of XP, the XPFSG has begun to undertake research that is hoped to have a more immediate effect on XP patients and their families. These efforts are spearheaded by Dr. Ijaz S. Jamall, Director of Research for the XPFSG, and briefly summarized in the following sections.

### 2.1. Solar UV risk assessment

One aspect of XPC, in particular, is the heightened vulnerability of these individuals to develop pre-cancerous and cancerous lesions, largely of the non-melanoma skin cancer (NMSC) type, notably, BCC and SCC upon exposure to sunlight. Most families in the US that are aware of their child’s diagnosis of XP go to considerable lengths to protect their children from any exposure to sunlight (UVR). As a consequence of this extraordinary effort by the families, XPC children in the US show far fewer NMSCs, for example, than that seen in XPC children in Barillas, Guatemala, as discussed above.

In the absence of any regulatory or biologically based standard of light exposure that could be deemed “tolerable” for XPC children, we propose using quantitative risk assessment modeling to develop a range of tolerable UVR doses that would allow parents of children with XPC to decide whether or not these estimates are acceptable to them. A major technical problem is that simple hand-held meters (e.g., Solarmeter made by Solartech Inc.) are designed to register only the carcinogenic wavelengths in the UVB range, but detect both UVA and UVB. Due to the overwhelming intensity of UVA in sunlight, variations in the meter readings do not accurately reflect variations in cancer risk.

There are algorithms to account for skin surface area exposed to solar UV, the age-adjusted frequency and duration of exposure, the UV dose by latitude and corrections for skin pigmentation [6–12].

Time-stamped, wristwatch like UVR dosimeters will be used to obtain a more accurate estimate of UVR dose [13–16].

## 2.2. Photocarcinogenicity of sunscreen ingredients

Earlier this summer, one of our XPFSG Board Members and a parent of children with XPC brought to our attention a letter addressed to the FDA by the Environmental Working Group suggesting that the presence of retinyl palmitate (RP), a vitamin A compound added to sunscreens, might pose a risk of accelerating skin cancers in people exposed to sunlight (<http://www.ewg.org/ewg-asks-fda-to-wind-up-study-of-vitamin-a-in-sunscreen>). We reviewed the peer-reviewed literature on the subject and summarized the literature through the XPFSG Newsletter to assist the XP community in making informed decisions about the use of sunscreens containing RP.

Over the past five years, several studies by the FDA and the National Toxicology Program (NTP) have demonstrated that the application of RP to the skin of rodents, as well as to human and other animal cells *in vitro* and exposed to UVR corresponding to simulated sun exposure causes DNA damage that could lead to skin cancers. Notably, these studies showed that the Vitamin A compounds by themselves did not cause DNA damage [17–21]. The DNA damage was observed only when UVR was introduced. The mechanism of this UV light-induced DNA damage has been shown to involve reactive oxygen species (ROS), a mechanism also shown to contribute to skin cancers following chronic sun exposure and a mechanism believed to contribute to skin cancers in non-XP and XP patients [14,22–24]. These findings were recently confirmed in a large scale mouse study by the National Toxicology Program (NTP). The study documented a dose-related increase in malignant skin cancers and suggested that low doses of sun exposure could initiate DNA damage in people exposed to RP (and other Vitamin A derivatives).

Wang et al. [25] defended the use of RP and other Vitamin A derivatives as being safe. Wang et al. raised the following key points. First, the authors claim that the NTP mouse study only shows a dose–response relationship between RP and low doses of solar radiation. Second Wang et al. claim that if sunscreens accelerate the development of skin cancers in people, why have rates not increased. But, between 1980 and 2004, the incidence of melanoma among young women increased by 50% from 9.4 cases to 13.9 cases per 100,000 women in the state of New York alone (<http://www.health.state.ny.us/statistics/diseases/cancer/skin/report/2009/>). Third, Wang et al. claim that Vitamin A compounds can be given orally with no carcinogenic response and note that oral isotretinoin was used successfully to prevent skin cancers in XP patients by Kramer et al. [26]. However, orally administered Vitamin A is not subjected to solar radiation and is, therefore, not relevant to the addition of Vitamin A compounds to sunscreens. Given that XPC patients have a documented defect in their DNA repair capability and are, as a consequence, more vulnerable to develop skin cancers, it would seem imprudent to use sunscreens containing Vitamin A compounds based on the available data.

## 2.3. Protective role of Vitamin D in XP

Insufficient serum levels of Vitamin D have been associated with increased incidence of cancers, including skin cancers [27–29]. The XPFSG has initiated a proof-of-concept study to determine if increasing serum 25(OH)D in XP patients can slow the onset, progression of skin cancers in XPC patients and also benefit the signs of neurological deficits in individuals with XPD. As a first step, we have begun to accumulate baseline serum 25(OH)D levels in the absence of any supplementation. In seven patients tested

thus far, four XPC patients had an average serum 25(OH)D level of 29.7 nmol/L (11.9 ng/mL). The baseline serum 25(OH)D levels in the three XPD patients was 29.0 nmol/L (11.6 ng/mL). In one male XPD patient in his late teens, his serum 25(OH)D was 29.3 nmol/L (11.7 ng/mL) in 2007 prior to treatment. At that time, he exhibited severe hand tremors making it difficult for him to drink from a cup or to control a pencil. The patient was put on oral vitamin D and calcium supplements such that his serum 25(OH)D increased to 93 nmol/L (37.3 ng/mL) in 2009. The tremors have completely gone, per his parents and attending neurologist (personal communications, 2008–2010). The goal is for patients to attain and maintain serum 25(OH)D levels of between 80 and 100 nmol/L (32–40 ng/mL), on average, to prevent vitamin D insufficiency [30].

## 2.4. Role of selenium in XP

XPFSG is initiating a proof-of-concept study with the hypothesis that XP individuals have markedly lower selenium levels than age-matched non-XP individuals. In the past three years, selenium-containing compounds have been shown to be very effective in the reduction of malignant melanoma, the skin cancer with the least favorable outcome in humans. The protective effects of selenium were shown to result from the ability of selenium to facilitate cell suicide (“apoptosis”) so they could not go on to become cancerous [31–35]. As a first step in deciding whether oral selenium might mitigate the onset and/or frequency of development of skin cancers in XP patients, the XPFSG will assess the selenium status of XP individuals and their non-XP relatives living in the same household so that any nutritional variability can be ruled out. This is most easily done by sampling scalp hair as has been done in Acrodermatitis enteropathica, an autosomal recessive zinc deficiency disorder [36].

## 3. Summary

The XPFSG has in its brief existence made considerable strides in reaching out to XP families in the US and in Guatemala and has undertaken significant clinical programs, developed new diagnostic techniques, and begun proof-of-concept clinical initiatives that could benefit patients and their families in the near term. The XPFSG works closely with the Owl Patrol, the UK XP Support Group led by Sandra Webb and the XP Support Group in Germany.<sup>1</sup>

## Conflict of interest

The authors have no conflict of interest.

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<sup>1</sup> The designation of the XP group assigned has come from a variety of sources, including the recent development of a simple immunohistochemical antibody staining method designed to identify XPC ([2], PMID 19915453) and other standard complementation and sequencing methods.

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