National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

XERODERMA PIGMENTOSUM: When the lifeguard of the gene pool goes on strike

Kenneth H Kraemer, M.D.

Laboratory of Cancer Biology and Genetics

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Bethesda, MD

Nov 15, 2022

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Debby Tamura R.N.
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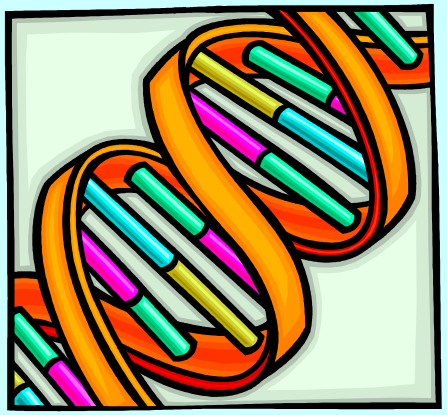

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Staff Scientist

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Kenneth H Kraemer, M.D.

I do not have any relevant relationships with industry.

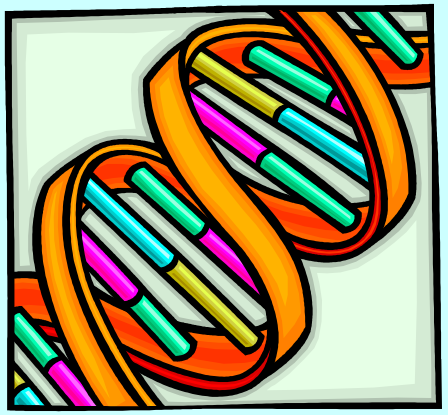
WHY STUDY RARE HUMAN GENETIC DISEASES?

Importance of Natural History Studies

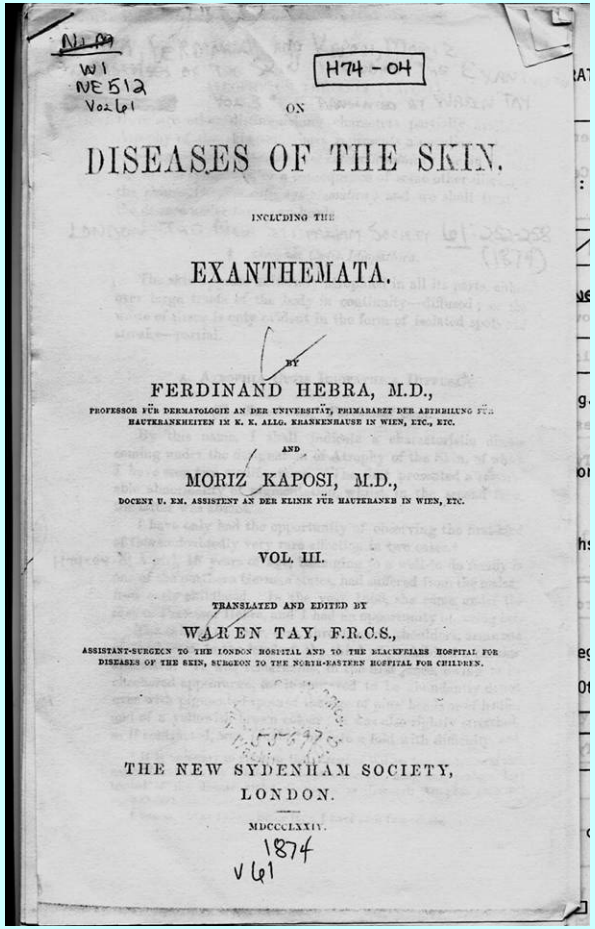
- CARE FOR AFFECTED PATIENTS
- DISCOVER MECHANISMS OF DISEASE
- DOCUMENT BASELINE PARAMETERS - USE FOR COMPARISON WITH FUTURE TREATMENTS
- DEVELOP NEW THERAPEUTIC PARADIGMS: USING SMALL NUMBERS OF PATIENTS AT HIGH RISK OF CANCER

Outline

- Early history of xeroderma pigmentosum (XP)
- NIH studies of XP and trichothiodystrophy (TTD) – clinic to laboratory and back
- Molecular Epidemiology
- Patient Management



FIRST DESCRIPTION OF XERODERMA PIGMENTOSUM
1874 - MORIZ KAPOSI



W1
NE512
Vol 61

H74-04

ON

DISEASES OF THE SKIN.

INCLUDING THE

EXANTHEMATA.

BY

FERDINAND HEBRA, M.D.,

PROFESSOR FÜR DERMATOLOGIE AN DER UNIVERSITÄT, PRIMARARZT DER ABTHEILUNG FÜR HAUTKRANKHEITEN IM K. K. ALLG. KRANKENHAUSE IN WIEN, ETC., ETC.

AND

MORIZ KAPOSI, M.D.,

DOCENT U. EM. ASSISTENT AN DER KLINIK FÜR HAUTKRANKH IN WIEN, ETC.

VOL. III.

TRANSLATED AND EDITED BY

WARREN TAY, F.R.C.S.,

ASSISTANT-SURGEON TO THE LONDON HOSPITAL AND TO THE BLACKFRIARS HOSPITAL FOR DISEASES OF THE SKIN, SURGEON TO THE NORTH-EASTERN HOSPITAL FOR CHILDREN.

THE NEW SYDENHAM SOCIETY,
LONDON.

MDCCCLXXIV.

1874
V61

Moriz Kohn 1837 - 1902

1953 – Watson and Crick describe double helix DNA structure

1964 – Richard Setlow and Phil Hanawalt separately describe DNA repair replication in bacteria

1968 – James Cleaver describes DNA repair defect in XP

Defective Repair Replication of DNA in Xeroderma Pigmentosum

by

J. E. CLEAVER

Laboratory of Radiobiology,
University of California Medical Center,
San

NATURE, VOL. 218, MAY 18, 1968

Normal skin fibroblasts can repair ultraviolet radiation damage to DNA by inserting new bases into DNA in the form of small patches. Cells from patients with the hereditary disease xeroderma pigmentosum carry a mutation such that repair replication of DNA is either absent or much reduced in comparison to normal fibroblasts. Patients with xeroderma pigmentosum develop fatal skin cancers when exposed to sunlight, and so the failure of DNA repair in the skin must be related to carcinogenesis.

Kenneth Kraemer

- 1971 Joined United States Public Health service at NIH
- Dermatology Branch, National Cancer Institute

1971
Harlem Hospital, NY

1971 – NIH
US Public Health Service

2009

DR. JAY ROBBINS

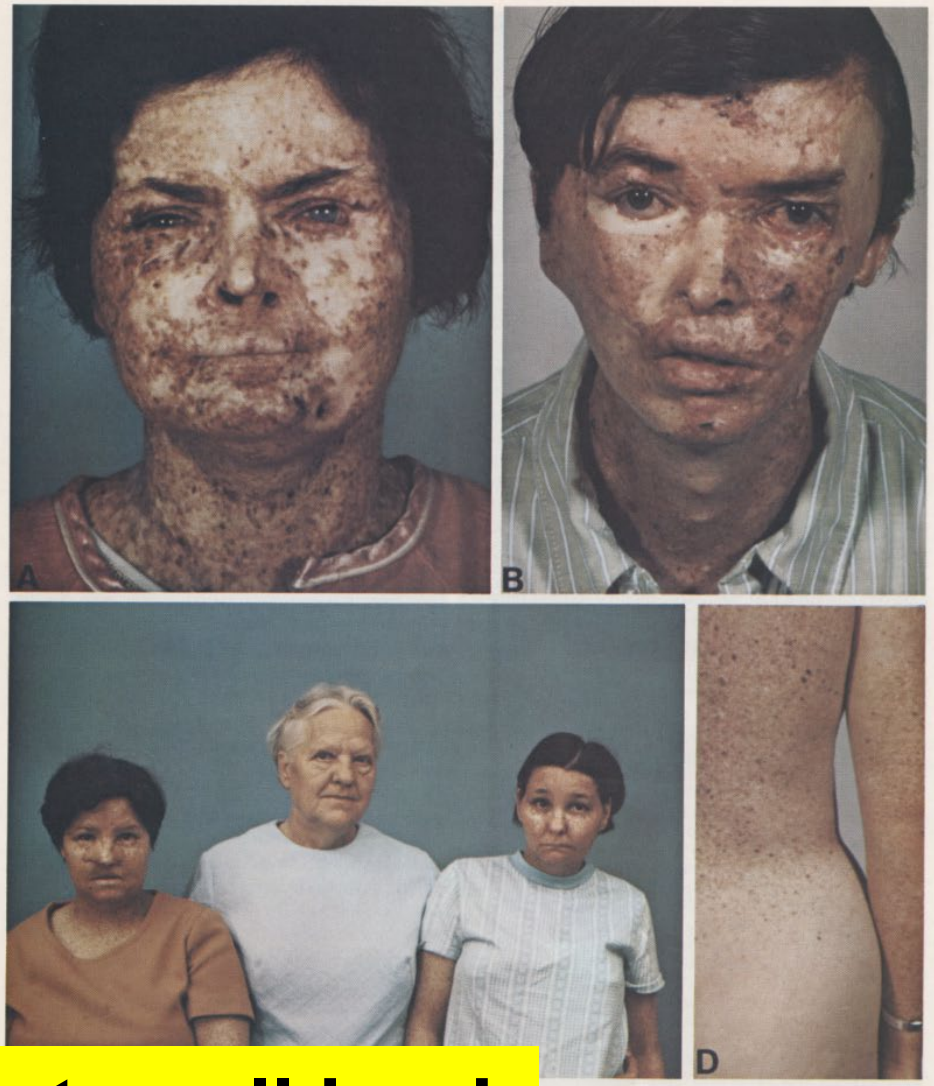
Reprinted from ANNALS OF INTERNAL MEDICINE Vol. 80, No. 2, Feb. 1974
Printed in U.S.A.

Xeroderma Pigmentosum

An Inherited Disease with Sun Sensitivity, Multiple Cutaneous Neoplasms, and Abnormal DNA Repair

Moderator: JAY H. ROBBINS, M.D. *Discussants:* KENNETH H. KRAEMER, M.D., MARVIN A. LUTZNER, M.D., BARRY W. FESTOFF, M.D., and HAYDEN G. COON, Ph.D,
Bethesda, Maryland

Detailed clinical and laboratory description of 15 XP patients – Varied phenotypes



DNA repair comprise four distinct complementation groups, indicating that at least four mutations can cause defective DNA repair.

DR. JAY H. ROBBINS*: Xeroderma pigmentosum is

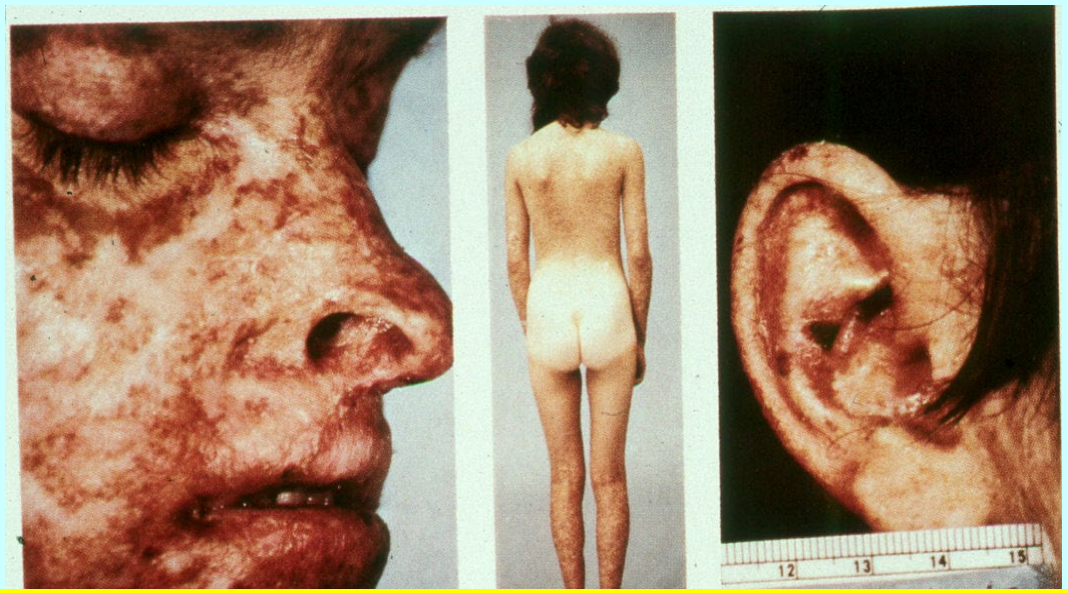
DNA-repair defect has been studied in fibroblast strains from approximately 60 patients with xeroderma pigmentosum. In the Dermatology Branch of the National Cancer Institute we have performed photobiological studies of the DNA-repair process in various types of cells from 15 of these patients, representing 12 kindreds (9-15). We have also evalu-

% of the normal DNA repair rate, show many of the cu- and numerous freckles with different intensities of pig- orneal transplant. The deformities of the nose and left , whose cells have no detectable defect in UV-induced igmentosum. The white, relatively disease-free areas of s obtained several years earlier from sun-protected, rela- a and the destruction of the left lower eyelid. C. Patient 55% of the normal DNA repair rate. The parents of pa- ease. The nose of Patient 5 has undergone several surgi- ions. D. Back and buttocks of Patient 6, showing the

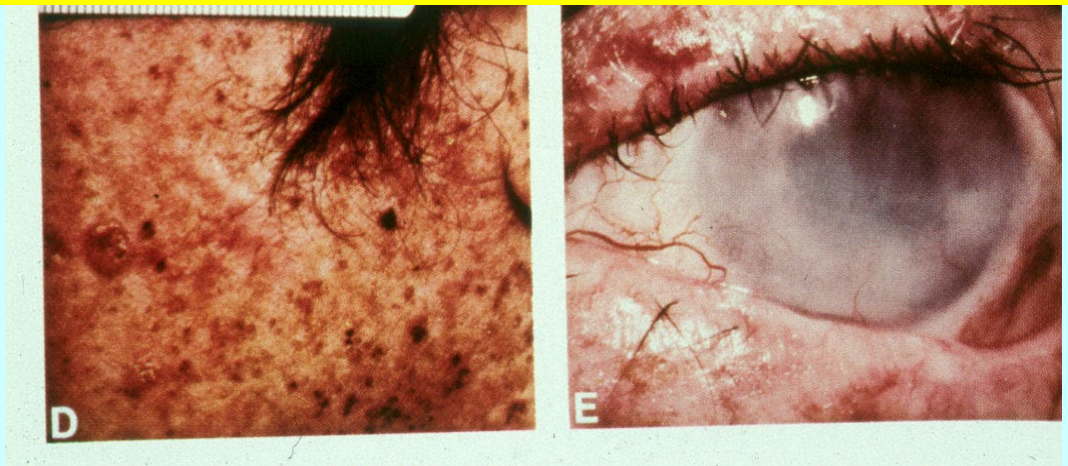
Donated cells from all patients to cell bank – made available to scientific community

Annals Int Med 1974

XERODERMA PIGMENTOSUM
CLINICAL FEATURES

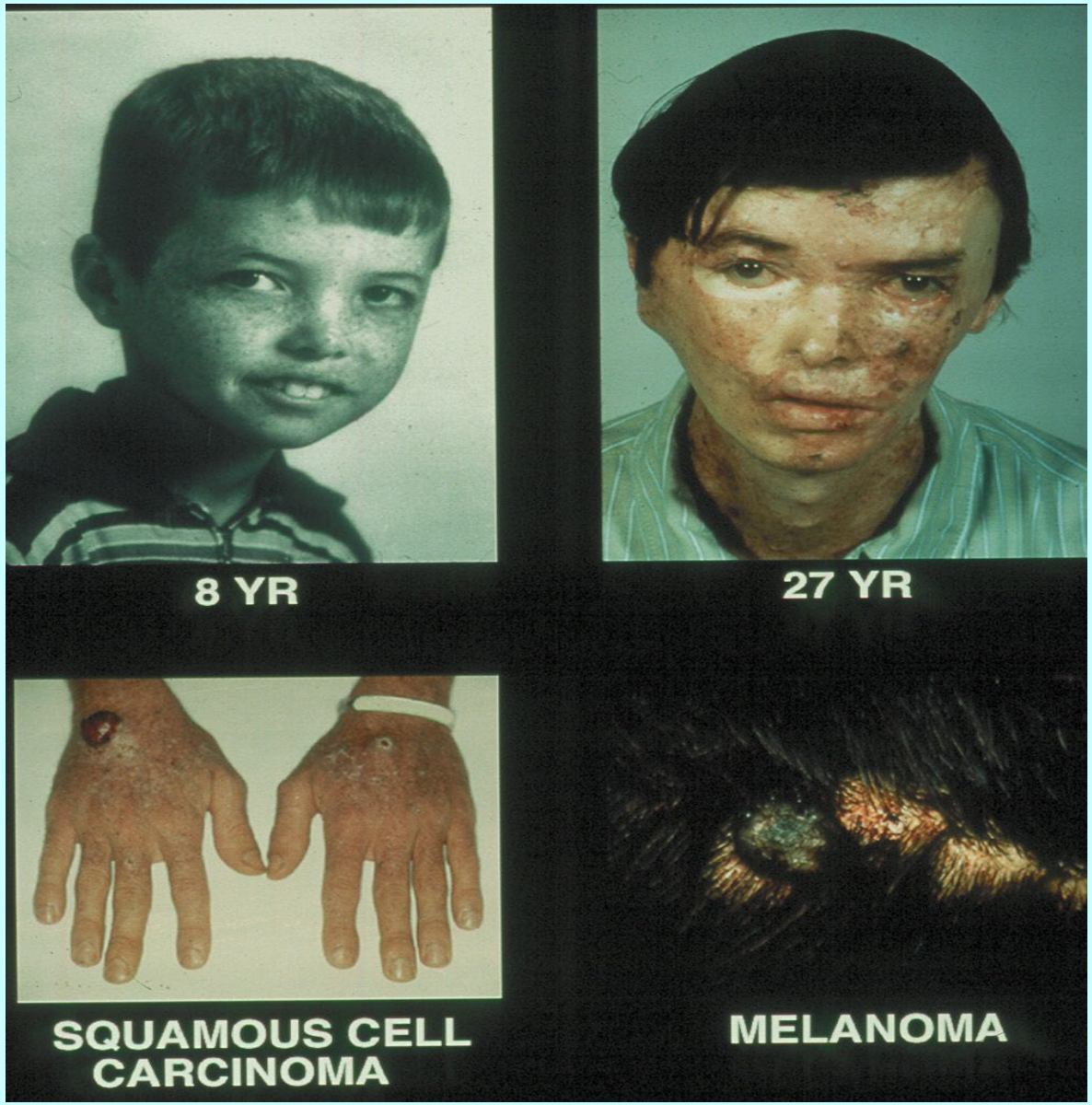


Premature photoaging of epidermis



Mol. Medicine
Today 5: 86 (1999)

XP VARIANT - XP4BE



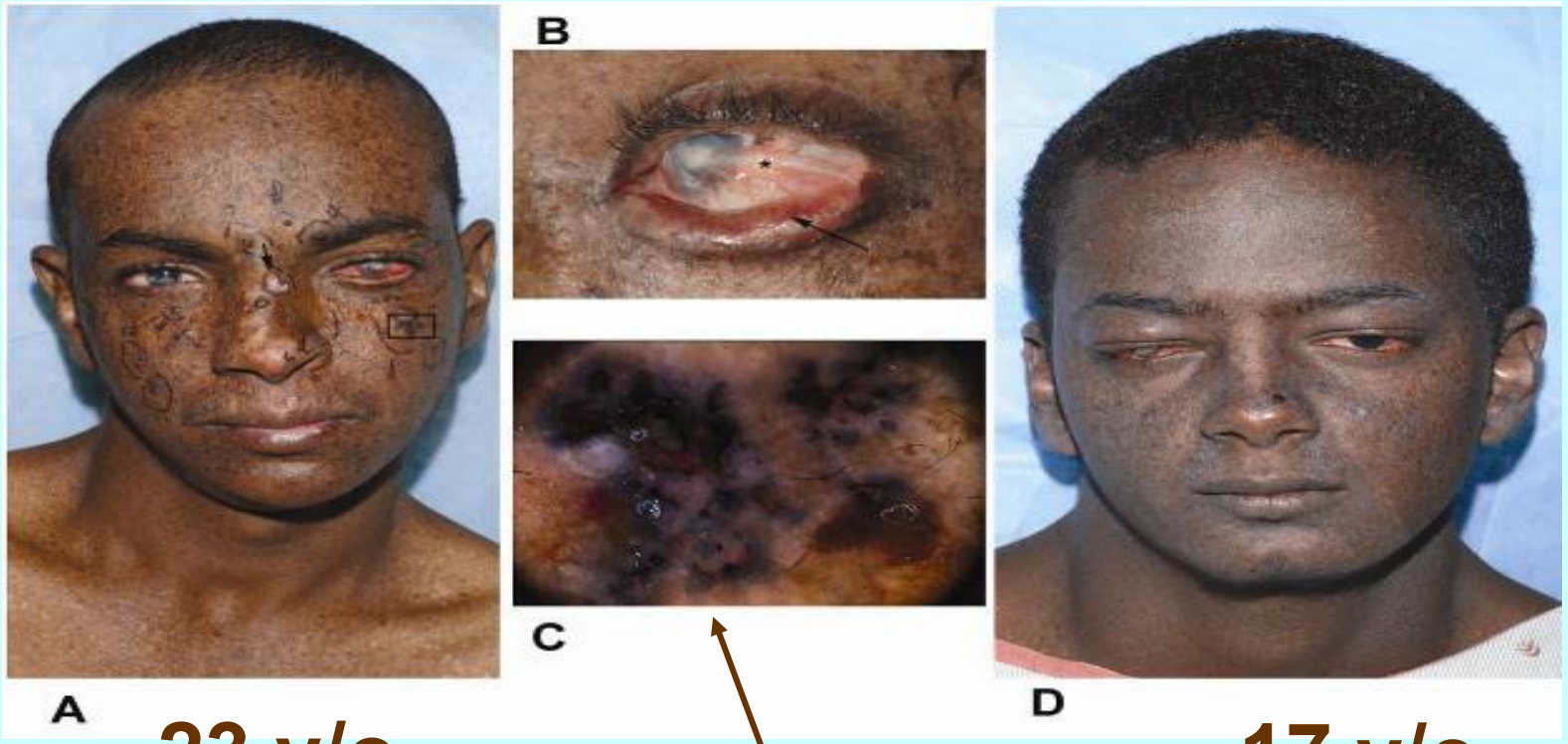
Polymerase eta defect

Died age 27 yr of metastatic melanoma

Multiple *PTEN* mutations in metastatic melanoma lesions

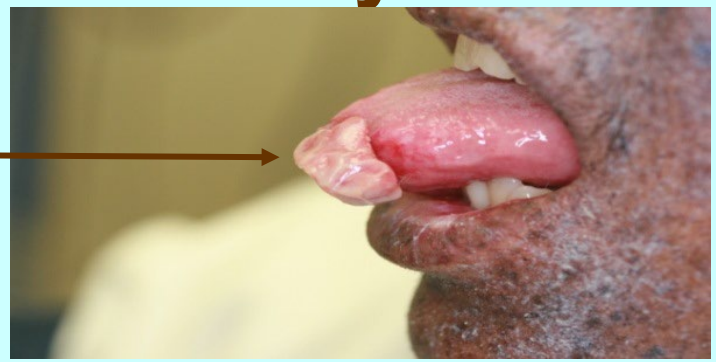
Wang et al JID 2009

AFRICAN BROTHERS WITH XERODERMA PIGMENTOSUM



23 y/o

17 y/o



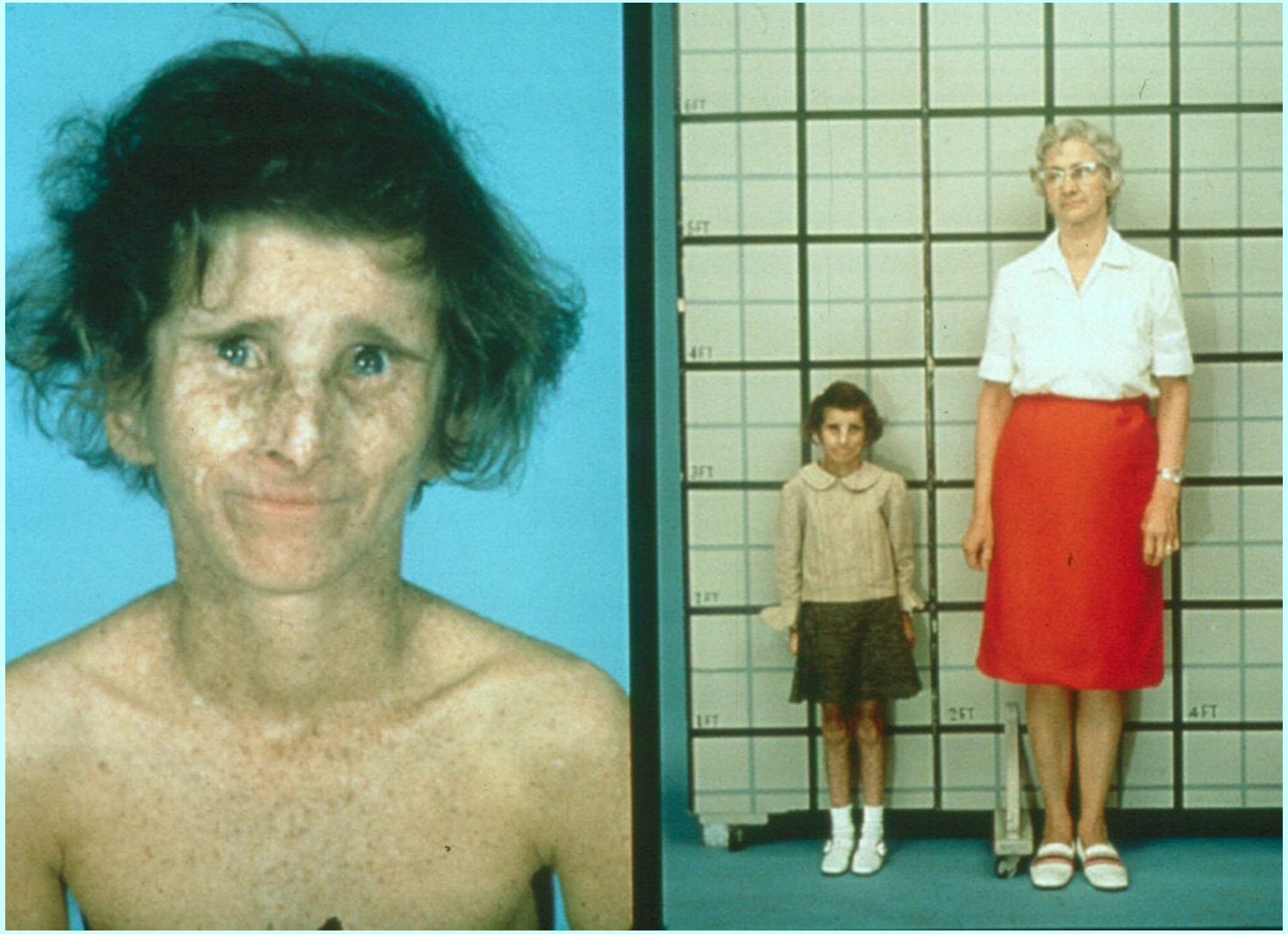
SCC

Pigmented BCC

XP reported in all races

Mahindra et al JAAD 59:881 (2008)

XERODERMA PIGMENTOSUM / COCKAYNE SYNDROME



XP/CS group B - XP11BE 28 yr Mother

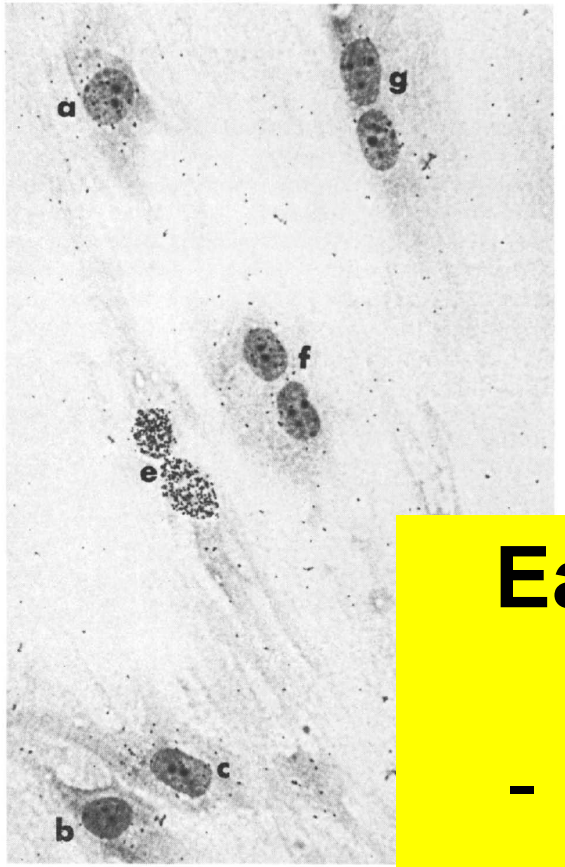
DR. DIRK BOOTSMA - ROTTERDAM

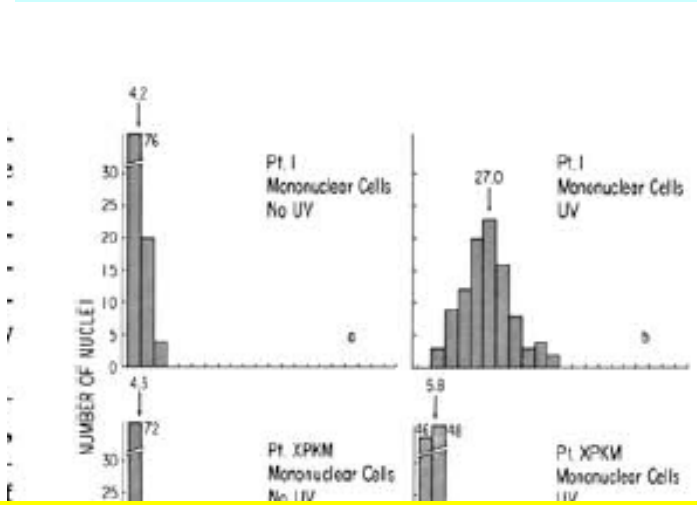
Reported 2 complementation groups in XP cells in 1972

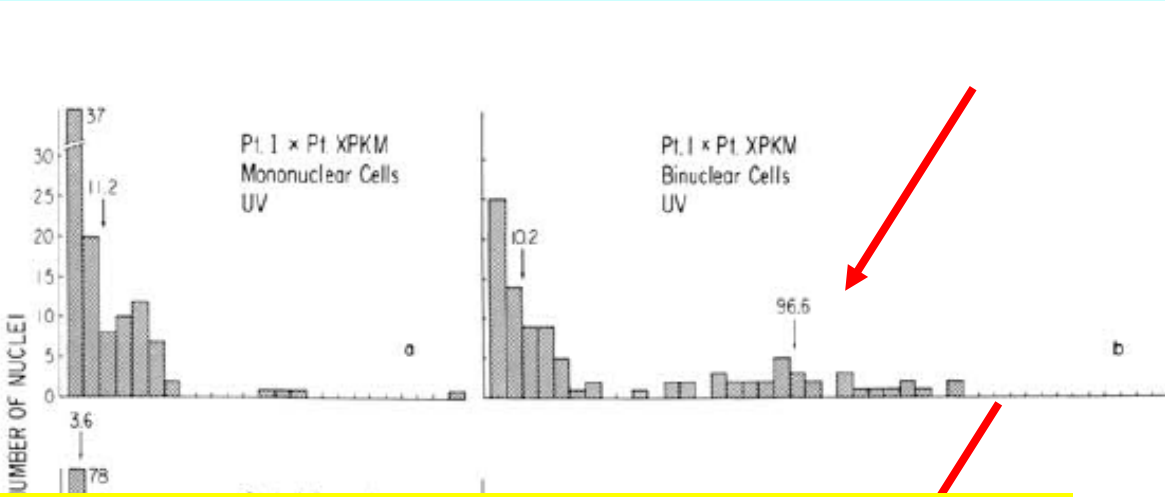
Genetic Heterogeneity of Xeroderma Pigmentosum demonstrated by Somatic Cell Hybridization
E. A. DE WEERD-KASTELEIN, W. KEIJZER & D. BOOTSMA
Nature New Biology 238: 80–83 (1972)

photo1994

AUTORADIOGRAPHY WITH CELL FUSION







Each cell supplies what the other is missing – they COMPLEMENT each other

- 3 complementation groups in Netherlands;

- 3 in NIH

Figure 9. Autoradiogram of unfused mon
(*a* to *d*) and of binuclear fibroblasts (e to g
treated culture containing cells from Patie
are in different complementation groups. The cells were exposed to 150 ergs/mm² of UV light and treated as described in the legend of Figure 3. The binuclear cell with numerous grains over its nuclei (*e*) is a heterokaryon whose nuclei have complemented each other, since both nuclei seem to have a normal or nearly normal amount of UV-induced ³HTdR incorporation, compared with the incorporation in the normal cells in Figure 3*B*. The other binuclear cells (*f* and *g*) are homokaryons, and their nuclei have no more incorporation than the nuclei of the unfused mononuclear cells (*a* to *d*). (Acid hematoxylin; magnification, × 420.)

10, 11 through 15, and so forth. Each arrow indicates the mean grain count for the 100 consecutively evaluated nuclei of each histogram, except that occasional cells with a high grain count that were apparently not in the grain distribution of the group evaluated were excluded (for example, the single cell in the 61-through-65 grain class of *d*). When more than thirty nuclei are in a single grain class, the bar representing them is truncated, and the number of cells in that class is printed above. See text for further description and interpretation.

donor. *D*. Irradiated mononuclear cells, not treated with virus, from the normal control donor. The grain distribution and mean grain count for the UV-induced ³HTdR incorporation into these normal cells (*d*) is approached by the complementing heterokaryons in *b*. One hundred nuclei were evaluated for each histogram, except that only fifty were evaluated for *d*. Details are explained in legend of Figure 11. See text for further description and interpretation.

Annals Int Med 1974

Mutation Research, 33 (1975) 327—340

FIVE COMPLEMENTATION GROUPS IN XERODERMA PIGMENTOSUM

K.H. KRAEMER[1], E.A. DE WEERD-KASTELEIN[2], J.H. ROBBINS[1], W. KEIJZER[2], S.F. BARRETT[1], R.A. PETINGA[1] AND D. BOOTSMA[2]

[1] *Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014 (U.S.A.) and* [2] *Department of Cell Biology and Genetics, Erasmus University, P.O. Box 1738, Rotterdam (The Netherlands)*

(Received July 24th, 1975)
(Accepted July 28th, 1975)

Summary

A collaborative study was undertaken to determine the relationship between the three DNA repair complementation groups in xeroderma pigmentosum found at Erasmus University, Rotterdam, and the four groups found at the National Institutes of Health, Bethesda. The results of this study reveal that there are five currently known complementation groups in xeroderma pigmentosum.

Introduction

Patients with xeroderma pigmentosum (XP) develop malignancies and pigmentation abnormalities on areas of skin exposed to sunlight [10]. Skin fibroblasts from most patients with this autosomal recessive disease are unable to perform excision repair of UV-induced pyrimidine dimers in their DNA as rapidly as normal fibroblasts [2,3,10]. This defective repair can be manifest as a decreased rate of UV-induced unscheduled DNA synthesis (UDS) [2,3,10]. In 1972 investigators at Erasmus University, Rotterdam, found two complementation groups in XP by showing that nuclei in heterokaryons formed by fusing fibroblasts from certain pairs of such repair-defective XP patients performed UV-induced UDS at a normal rate [11]. Subsequently a third complementation group was found among the Rotterdam XP strains [12].

The demonstration of genetic heterogeneity for DNA repair among the Rotterdam XP

Abbreviations: dine; NIH, Nat

5 complementation groups – named in order of increasing residual repair

Mutat Res1975

TABLE III

COMPARISON OF UV-INDUCED UDS IN THE REPRESENTATIVE XP STRAINS MEASURED IN BOTH INSTITUTES

Complementation group	Strain	UV-induced UDS (% of normal rate)	
		Rotterdam[a]	NIH[b]
A	Control donors	100	100
	XP25RO	<5	<2
	XP12BE		<2
	XP1LO	<5	<2
B	XP11BE	4	4.8
C	XP4RO	10—15	12.9
	XP1BE		19.8
	XP2BE	24—27	13—18
D	XP5BE	10	27.1
E	XP2RO	40—60	60

[a] Expressed as a percentage of the levels found in normal cells after a UV dose of 10 J/m^2.
[b] Expressed as a percentage of the levels found in normal cells after a UV dose of 30 J/m^2.

Co-operation/ collaboration among laboratories studying DNA Repair

Reprinted from the Archives of Dermatology
February 1987, Volume 123

Review Article

Xeroderma Pigmentosum

Cutaneous, Ocular, and Neurologic Abnormalities in 830 Published Cases

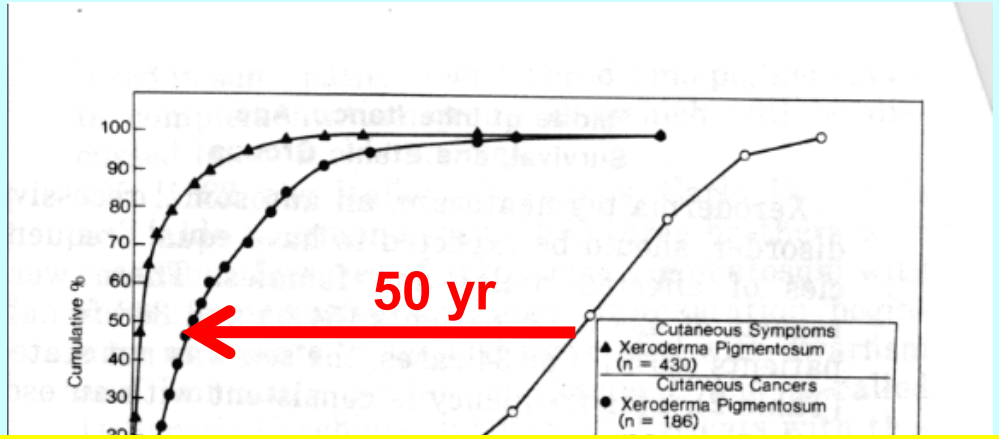
Kenneth H. Kraemer, MD; Myung M. Lee; Joseph Scotto, MS

• Quantitative frequencies of clinical abnormalities in xeroderma pigmentosum were estimated by abstracting published descriptions of 830 patients in 297 articles obtained from a survey of the medical literature from 1874 to 1982. The median patient age was 12 years with nearly equal numbers of male and female patients. Cutaneous symptoms (sun sensitivity or freckling) had a median age of onset of between 1 and 2 years. Forty-five percent of the patients described had basal cell carcinoma or squamous cell carcinoma of the skin. The median age of first nonmelanoma skin cancer among patients with xeroderma pigmentosum was 8 years, more than 50 years less than that among patients with skin cancer in the United States. Melanomas were reported in 5% of patients. Ninety-seven percent of the reported basal and

Xeroderma pigmentosum is a rare genetic disease with clinical and cellular hypersensitivity to ultraviolet radiation and defective DNA repair. Patients with xeroderma pigmentosum experience sun-induced cutaneous and ocular abnormalities, including neoplasia. Some patients have, in addition, progressive neurologic degeneration. Xeroderma pigmentosum, thus, serves as a model disorder linking defective DNA repair with clinical abnormalities and neoplasia. Quantitative information concerning the frequency of various clinical features of xeroderma pigmentosum would be useful in guiding patient management and in increasing understanding of the manifestations of defective DNA repair. To obtain

mental deterioration, hyporeflexia or areflexia, and progressive deafness in some patients in association with dwarfism and immature sexual development. There was

of xeroderma pigmentosum was prepared to probe for 207 items of clinical or laboratory information. A separate form was prepared for each patient mentioned in a report.



or pigmentation) was reported for 430 patients. Age at first skin cancer was reported for 186 patients and is compared with age

XP literature review – 830 patients

XP patients develop skin cancer 50 years earlier than in the general population

Strong evidence of the importance of DNA Repair in PREVENTION of skin cancer

Arch Derm 1987

Reprinted from the Archives of Dermatology
August, 1994 Volume 130

STUDY

The Role of Sunlight and DNA Repair in Melanoma and Nonmelanoma Skin Cancer

The Xeroderma Pigmentosum Paradigm

Kenneth H. Kraemer, MD; Myung-Moo Lee, MD; Alan D. Andrews, MD; W. Clark Lambert, MD, PhD

Background and Design: The frequency of melanoma and nonmelanoma skin cancer is increasing rapidly in the United States. However, the linkage of these cancers to sun exposure has been questioned because of differences in anatomic site distribution. To obtain insights into the development of these skin cancers, we examined reports of 132 patients with xeroderma pigmentosum (XP), an inherited cancer-prone, DNA repair–deficient disorder with

cancers (basal cell and squamous cell carcinomas), anterior eye cancers, and tongue cancers, but unlike that of internal neoplasms, was increased 1000-fold or more in patients with XP who were younger than 20 years. As in the general population, the anatomic distribution of melanomas was different from that of nonmelanomas in the patients with XP.

cell carcinoma, and 22% had melanoma. The frequency of melanomas, like the frequency of nonmelanoma skin

(Arch Dermatol. 1994;130:1018-1021)

XP Registry– 132 patients

THE FREQUENCY of both melanoma and nonmelanoma skin cancer is increasing rapidly in the United States.[1-3] The degree of asso-

group was young, with a median age of 16 years; 123 of the patients were younger than 40 years. Malignant skin neoplasms were reported in 93 (70%) of the patients. The median age for development of

70% had skin cancer – median age 8 years

Dermatology, Columbia University College of Physicians and Surgeons, New York, NY (Dr Andrews); and the Departments of Laboratory Medicine and Pathology and Dermatology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ (Dr Lambert). Dr Lee is now with the Division of Dermatology, Department of Family Practice, US Air Force Medical Corps, Yokota (Japan) Air Base Hospital.

marked clinical and cellular UV hypersensitivity and defective DNA repair in all cells, develop numerous skin cancers.[4-7] In a search for insight into factors that are important in the development of melanoma and nonmelanoma skin cancers in humans, we analyzed information obtained from reports to the Xeroderma Pigmentosum Registry, Newark, NJ.

tiple skin cancers: 73 patients had more than one cancer (20 of these had both basal cell carcinoma and melanoma), and 32 patients had more than 20 skin cancers each (based on the 82 reports in which the number of skin cancers was specified).

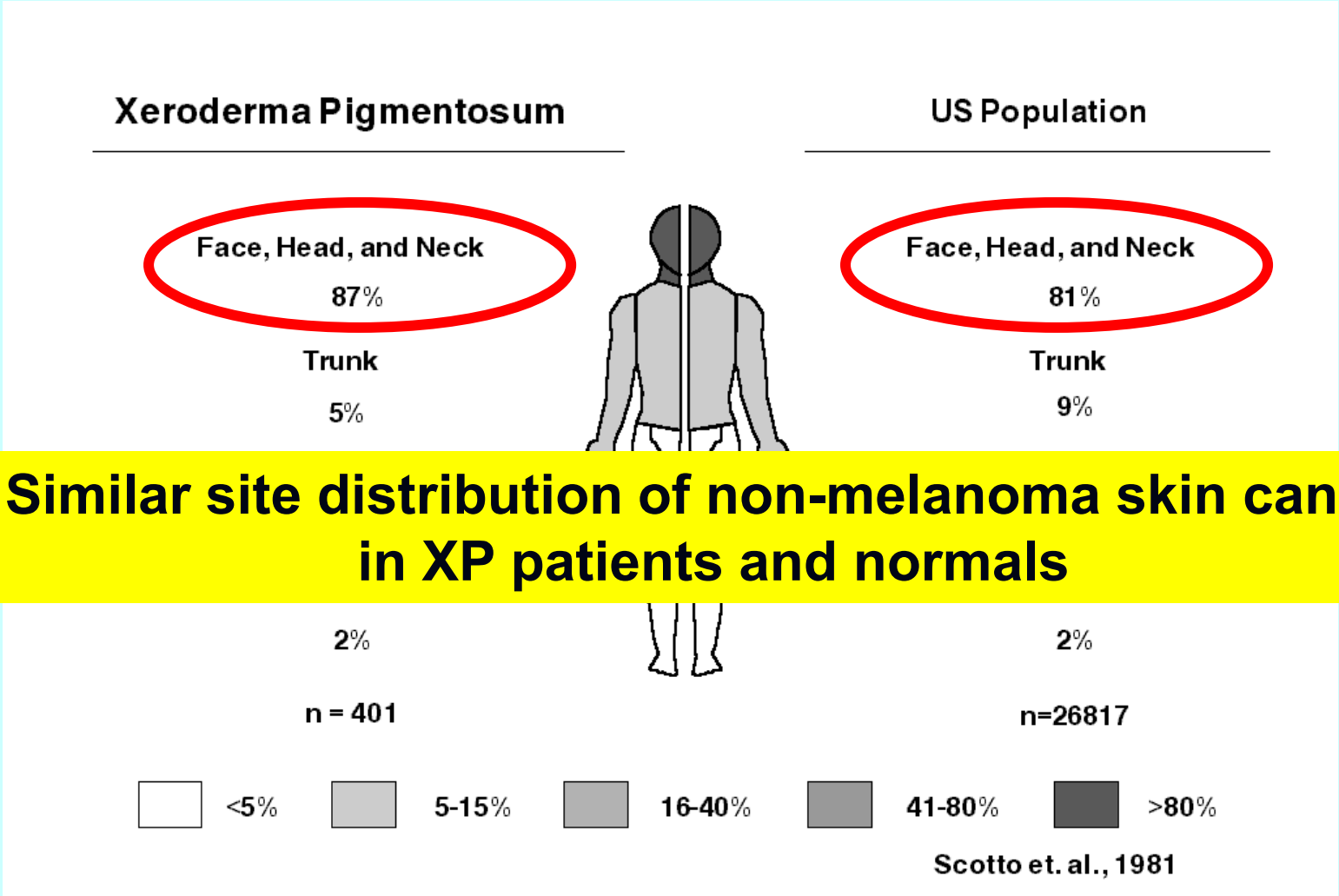
RESULTS

A total of 132 patients with XP were registered: 72 males and 60 females. The

See Methods on next page

Arch Derm 1994

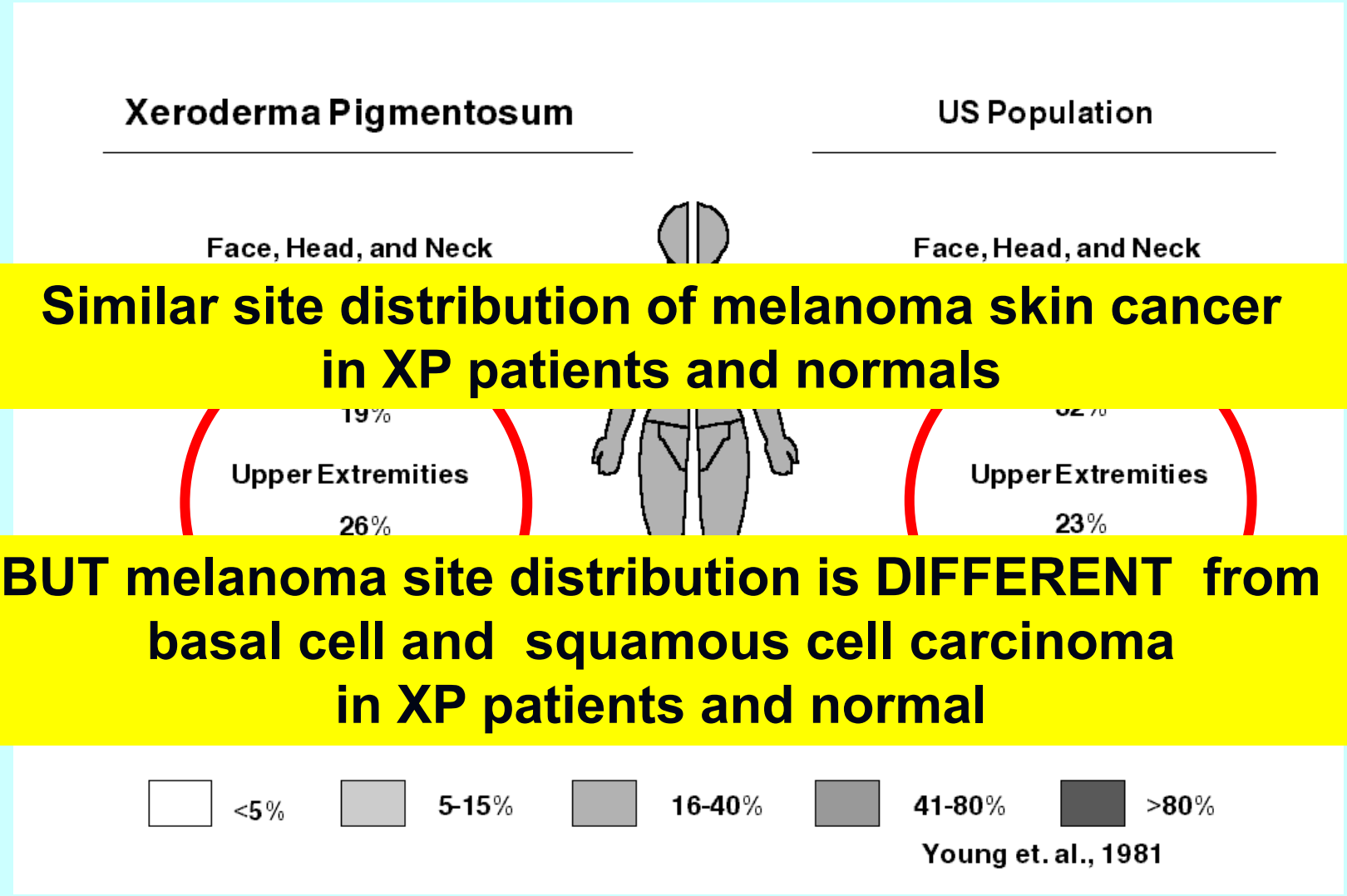
SITES OF BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA IN XP AND NORMALS



Similar site distribution of non-melanoma skin cancer in XP patients and normals

Arch Dermatol 130: 1018 (1994)

SITES OF MELANOMA IN XP AND NORMALS

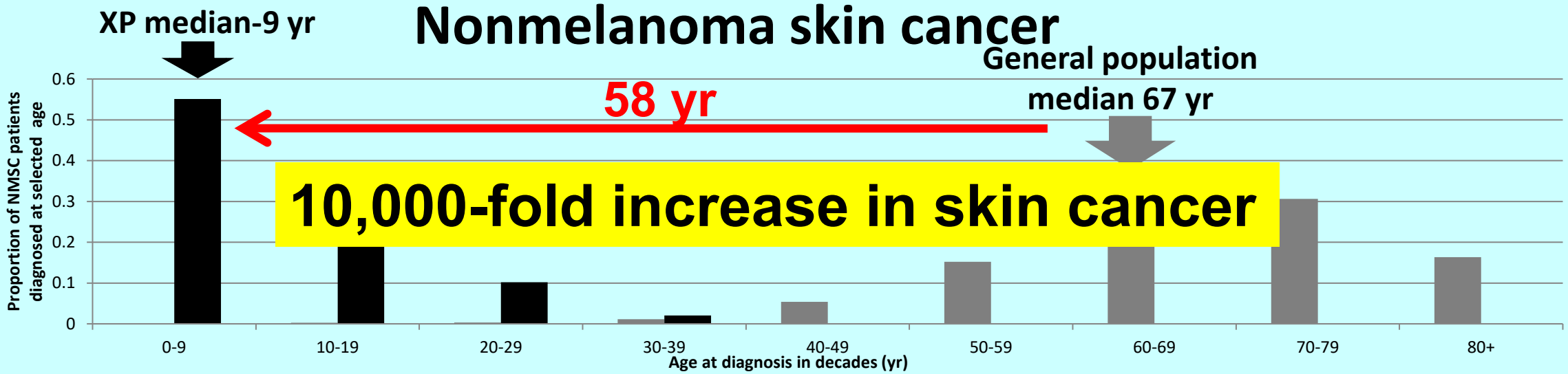


Similar site distribution of melanoma skin cancer in XP patients and normals

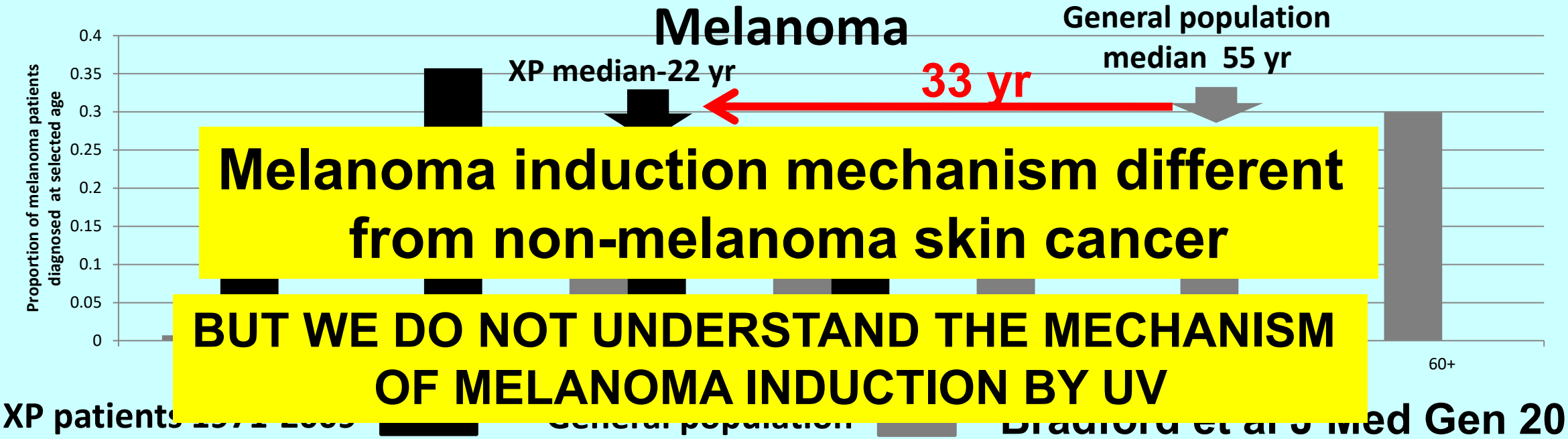
BUT melanoma site distribution is DIFFERENT from basal cell and squamous cell carcinoma in XP patients and normal

Arch Dermatol 130:1018 (1994)

EARLY AGE OF ONSET OF SKIN CANCER IN XERODERMA PIGMENTOSUM



10,000-fold increase in skin cancer



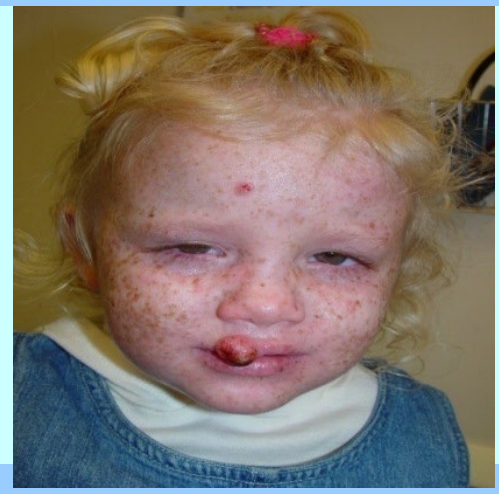
Melanoma induction mechanism different from non-melanoma skin cancer

BUT WE DO NOT UNDERSTAND THE MECHANISM OF MELANOMA INDUCTION BY UV

106 XP patients [illegible] Bradford et al J Med Gen 2010

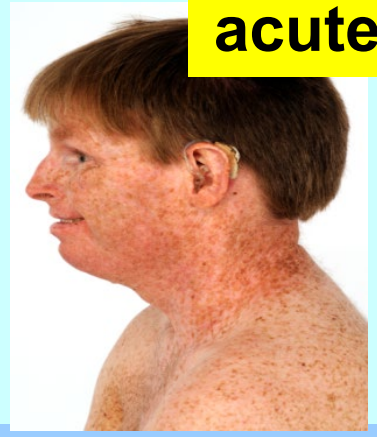
PHOTOSENSITIVE AND NON-PHOTOSENSITIVE XP PATIENTS

XP-D Age 9 mo
photosensitive

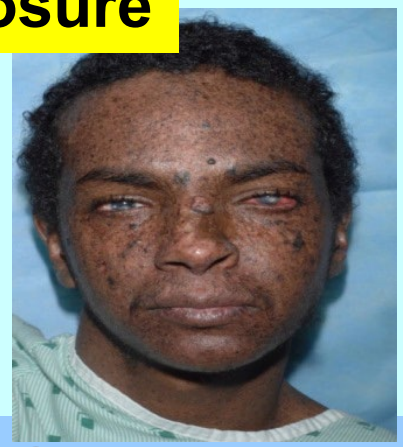


XP-C Age 2 yr
sensitive

About 50% of XP patients have acute burning on minimal sun exposure



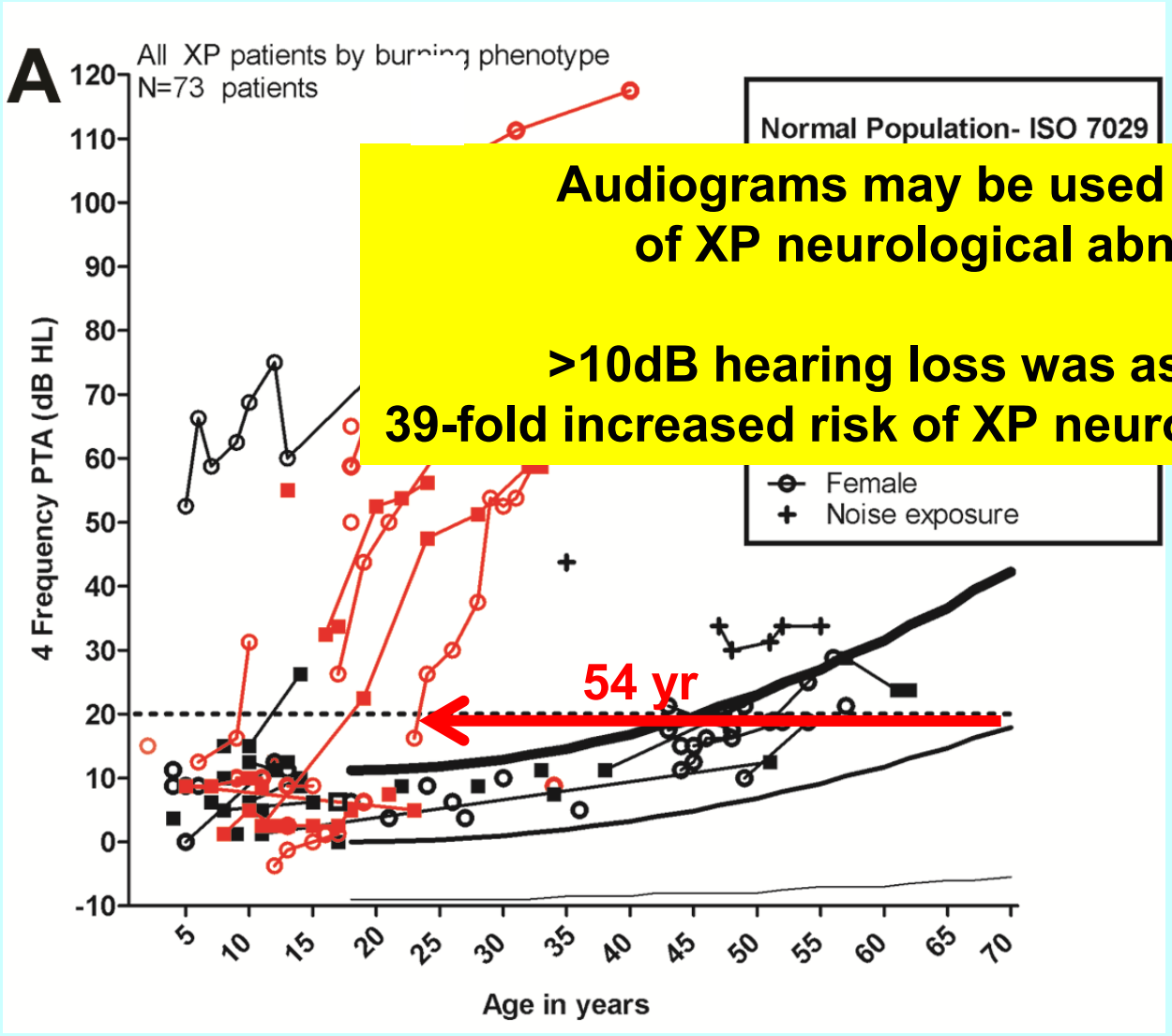
Bradford et al
J Med Gen 2010



XP-A Age 35 yr
photosensitive

XP-C Age 23 yr
Non-photosensitive

40 YEARS FOLLOW-UP OF XERODERMA PIGMENTOSUM AT NIH
HEARING LOSS AND ACUTE BURNING ON MINIMAL SUN EXPOSURE ARE PREDICTORS OF PROGRESSIVE NEUROLOGICAL DEGENERATION (n=73)



Audiograms may be used as predictors of XP neurological abnormalities:

>10dB hearing loss was associated with 39-fold increased risk of XP neurological degeneration

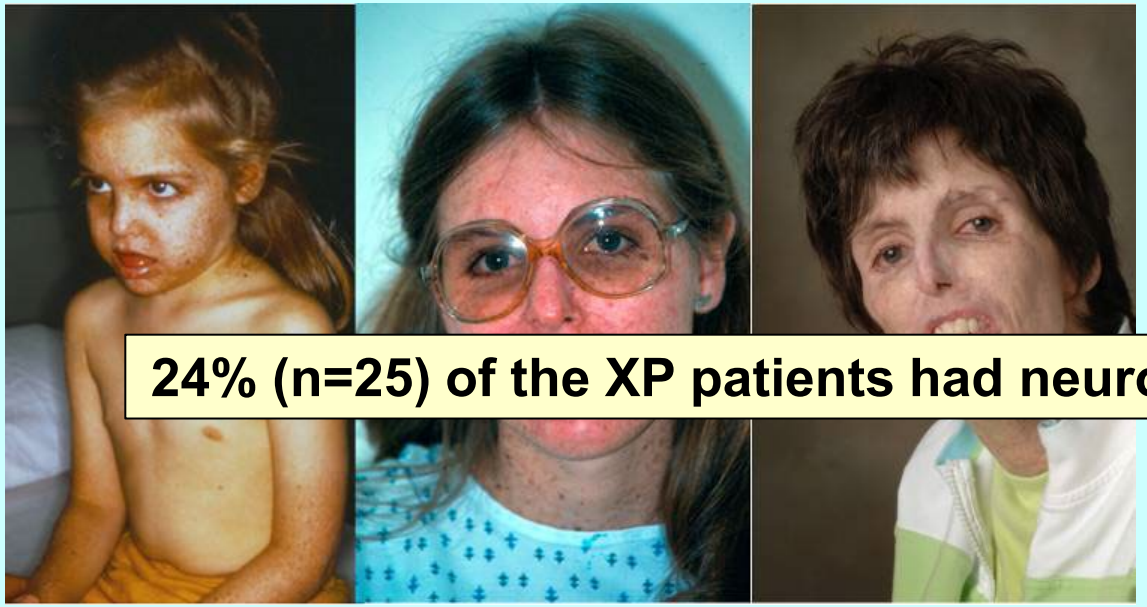
BRAIN
A JOURNAL OF NEUROLOGY 2013

Mariam B. Totonchy, Deborah Tamura, Matthew S. Pantell et al.

Auditory analysis of xeroderma pigmentosum 1971–2012: hearing function, sun sensitivity and DNA repair predict neurological degeneration

Totonchy DiGiovanna.. Kraemer Brain 2013

40 YEARS FOLLOW-UP OF XERODERMA PIGMENTOSUM AT NIH
PROGRESSIVE NEURODEGENERATION with BRAIN ATROPHY



4 yr 17 yr 41 yr

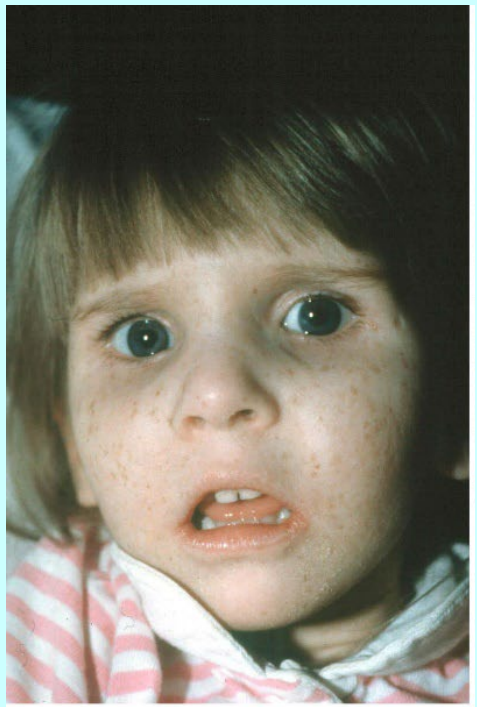
XP12BE
– XP-A
death age 44

24% (n=25) of the XP patients had neurodegeneration

Bradford..DiGiovanna..Kraemer. J Med Gen 2010

XP-G PATIENTS – SEVERE and MILD DISEASE

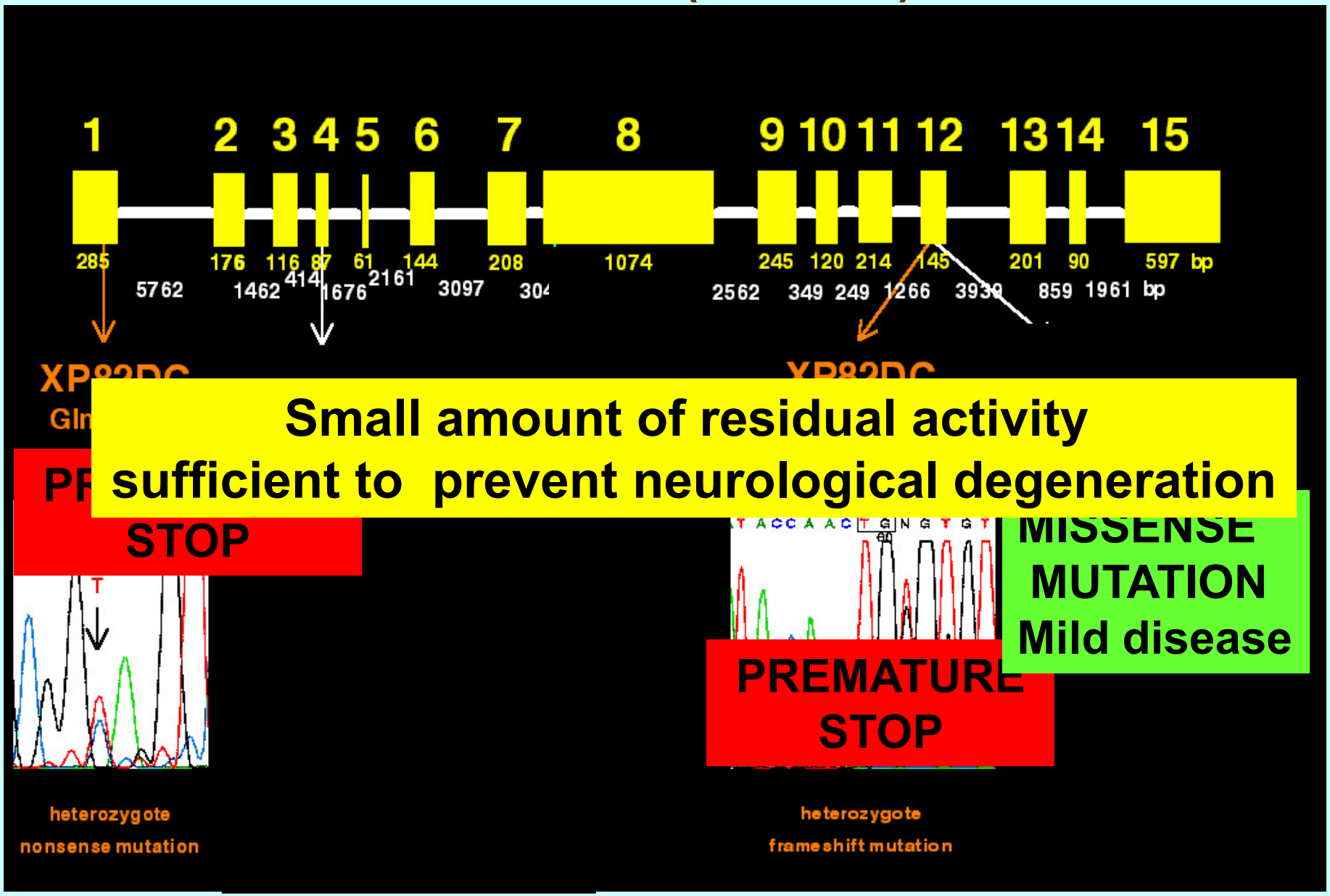
XP/CS
Died age 6 y/o



XP82DC – 3 y/o

Emmert et al J Invest Dermatol (2002)

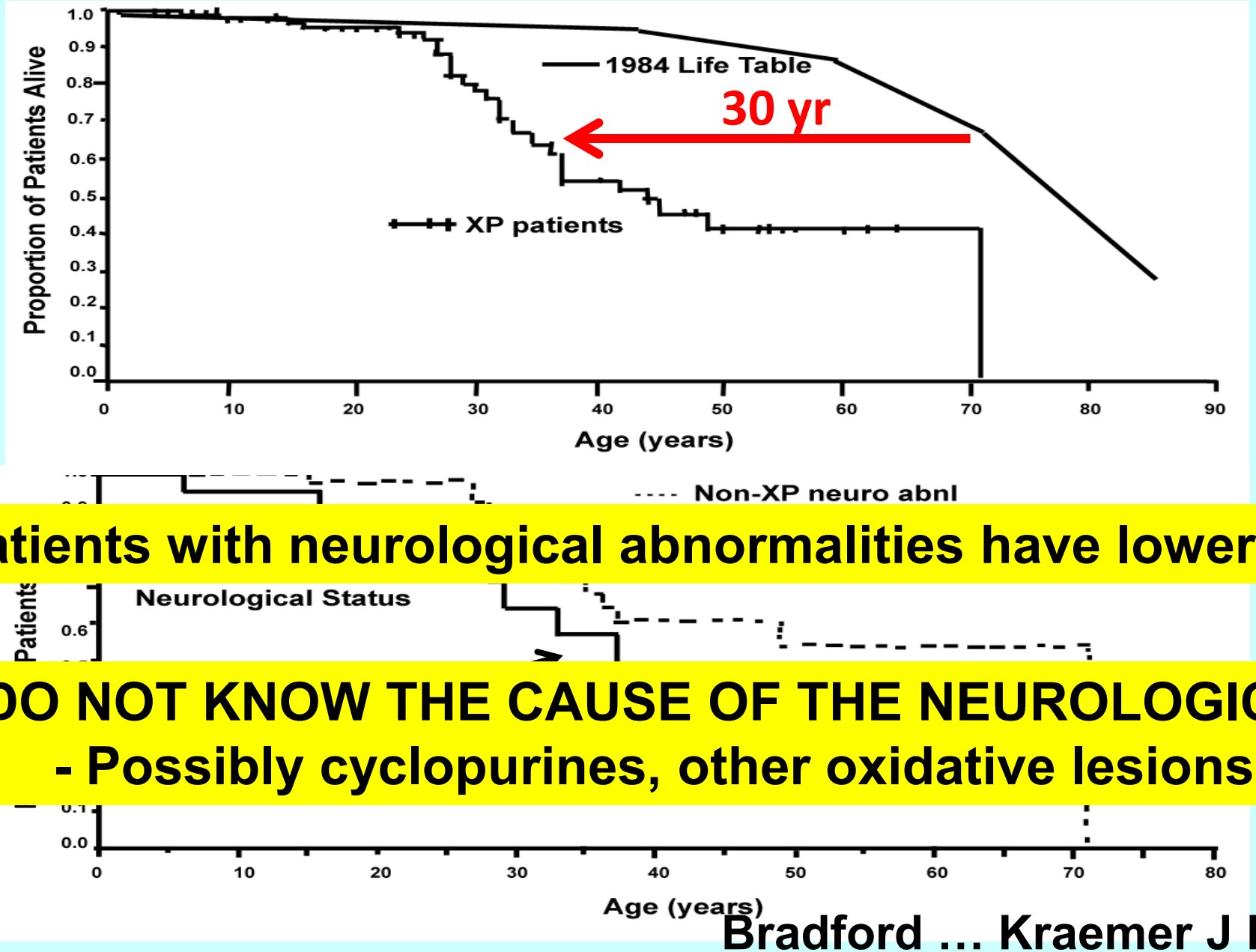
MUTATIONS IN *XPG* (*ERCC5*) GENE



Emmert et al J Invest Dermatol (2002)

40 YEARS FOLLOW-UP OF XERODERMA PIGMENTOSUM AT NIH

REDUCED SURVIVAL IN XERODERMA PIGMENTOSUM



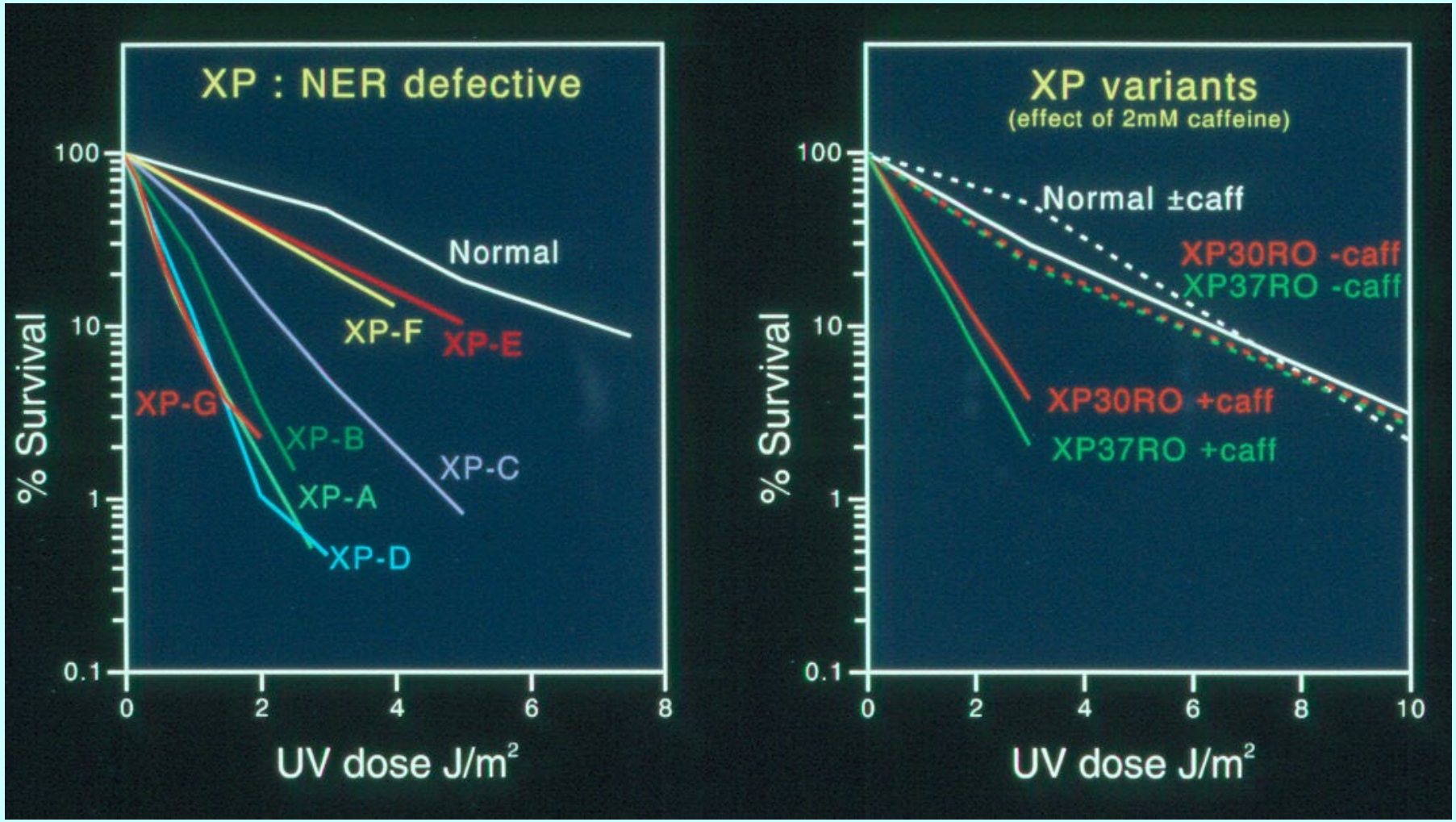
XP patients with neurological abnormalities have lower survival

BUT WE DO NOT KNOW THE CAUSE OF THE NEUROLOGICAL DAMAGE

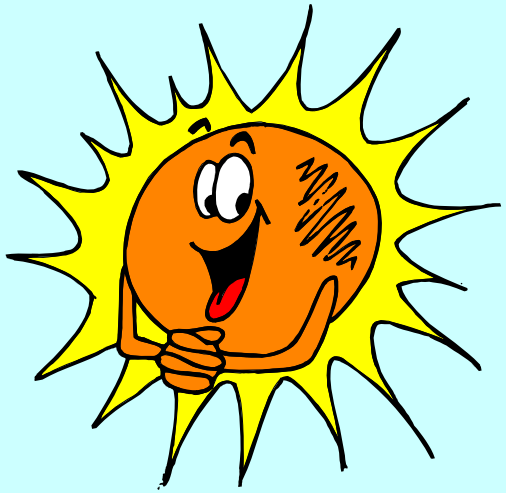
- Possibly cyclopurines, other oxidative lesions?

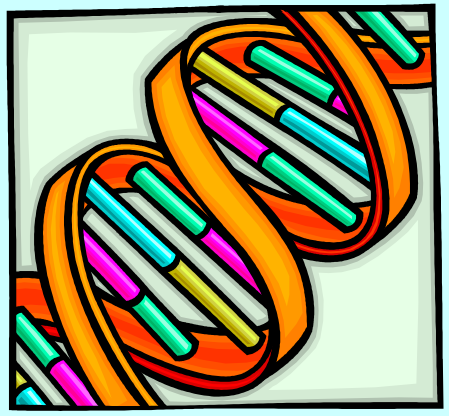
Bradford … Kraemer J Med Gen 2010

UV HYPERSENSITIVITY OF XERODERMA PIGMENTOSUM CELLS

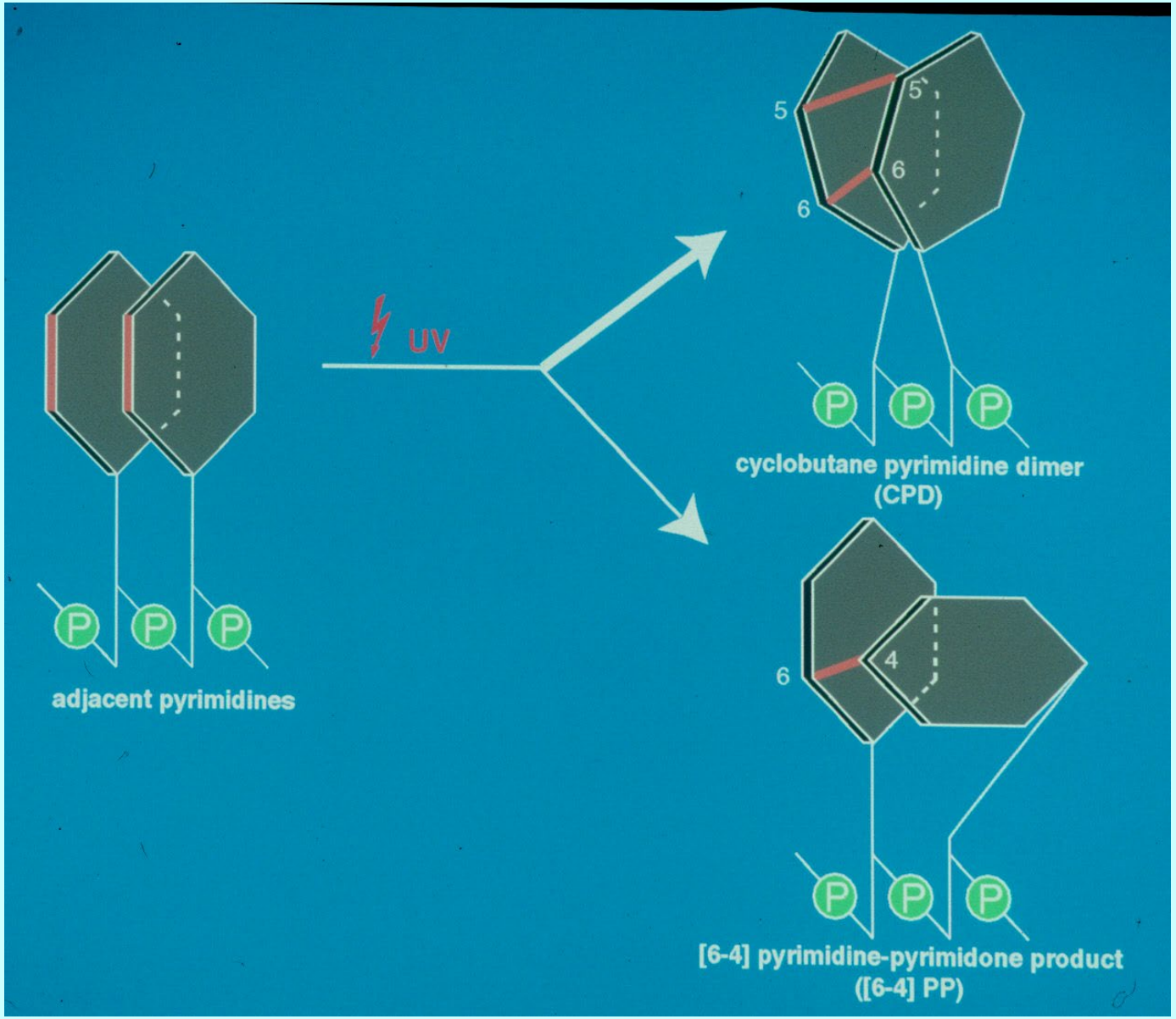


DNA REPAIR –
THE LIFEGUARD OF THE GENE POOL

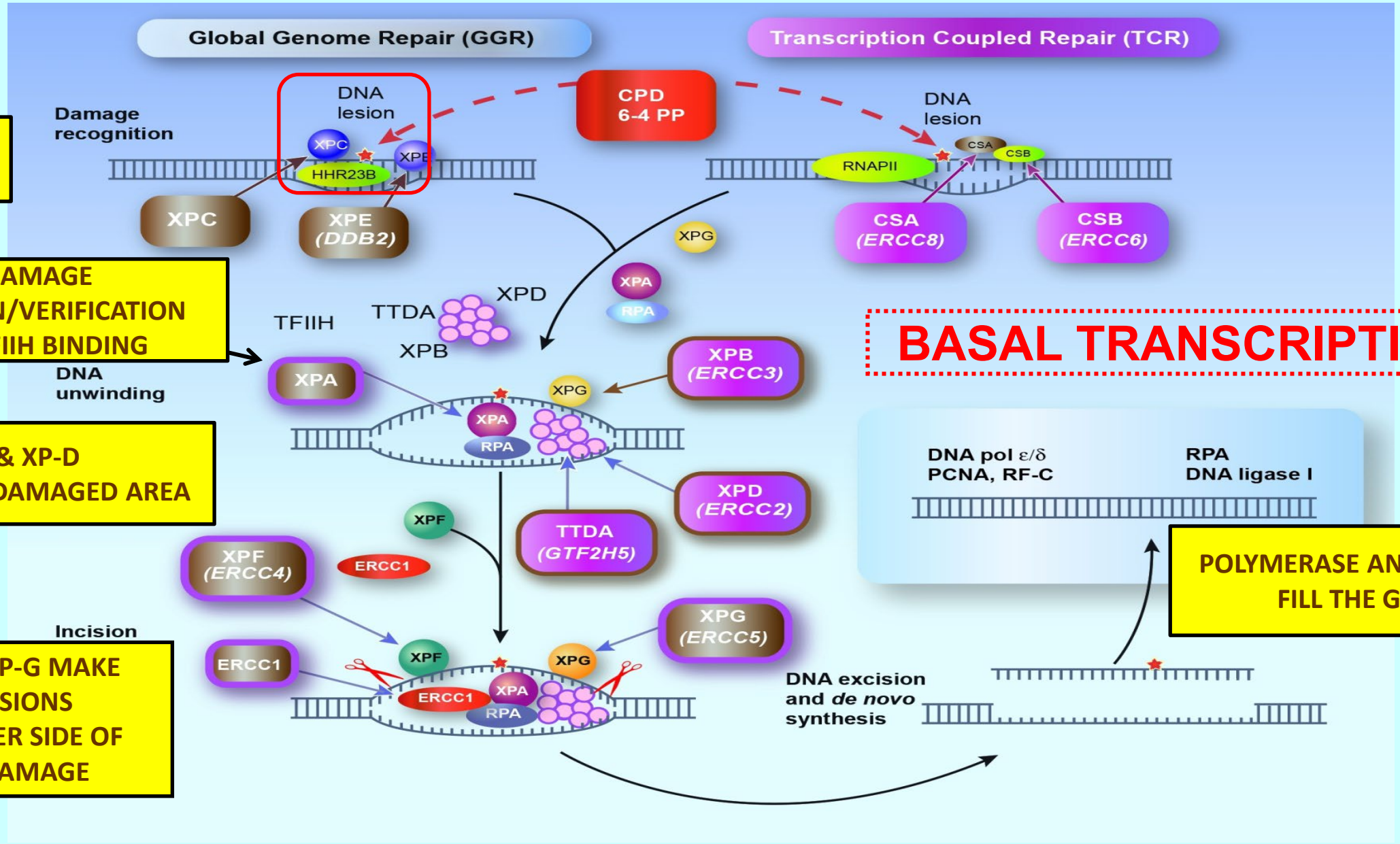




UV PHOTOPRODUCTS



NUCLEOTIDE EXCISION REPAIR PATHWAY



XP-C & XP-E

XPA DAMAGE RECOGNITION/VERIFICATION BEFORE TFIIH BINDING

XP-B & XP-D UNWIND THE DAMAGED AREA

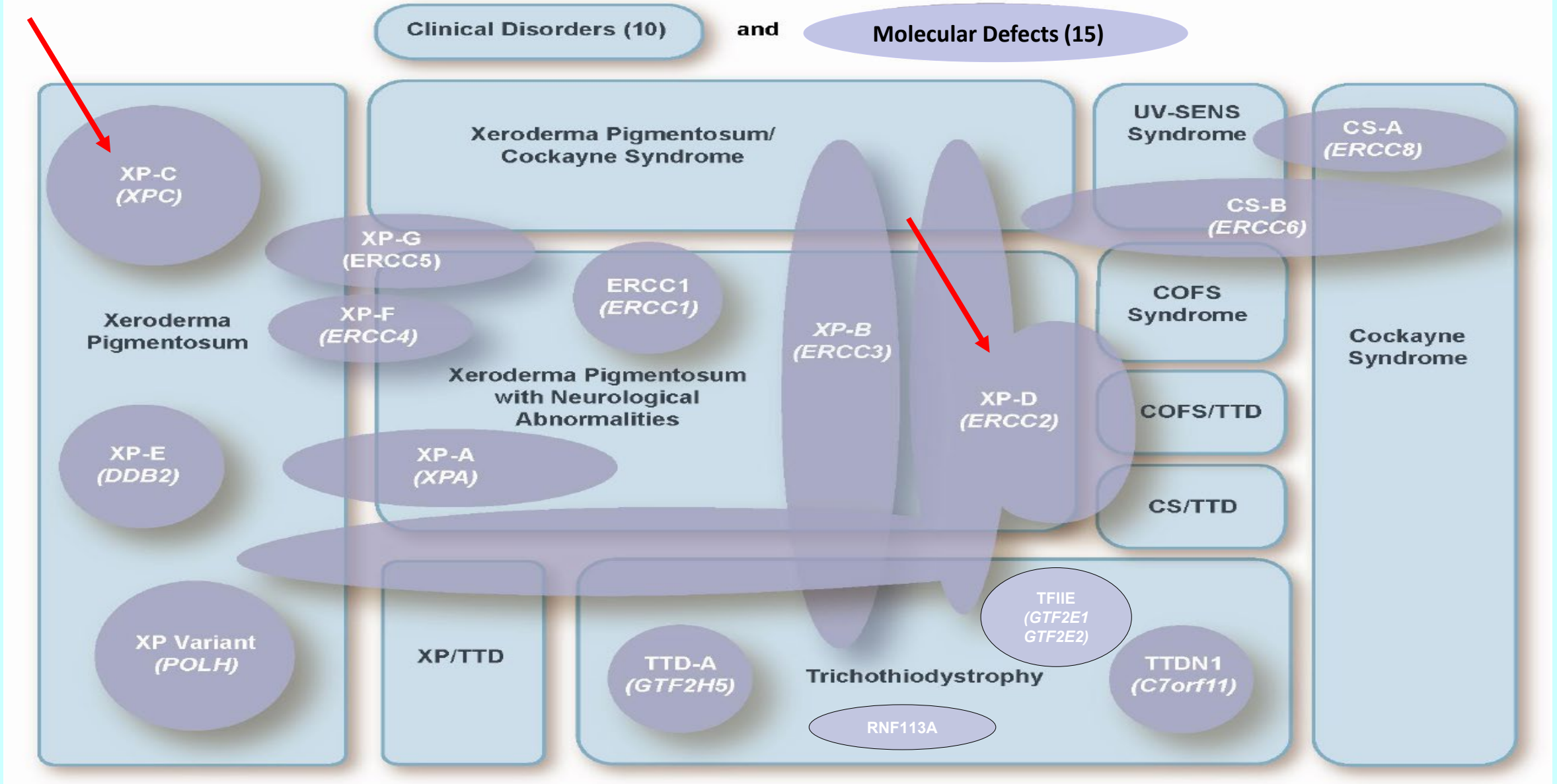
XP-F & XP-G MAKE INCISIONS ON EITHER SIDE OF THE DAMAGE

BASAL TRANSCRIPTION

POLYMERASE AND LIGASE FILL THE GAP

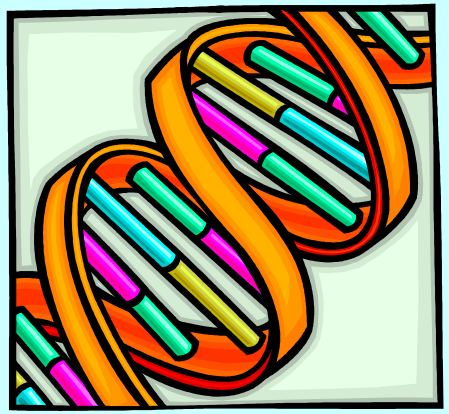
DiGiovanna and Kraemer JID 2012

DNA REPAIR DISORDERS

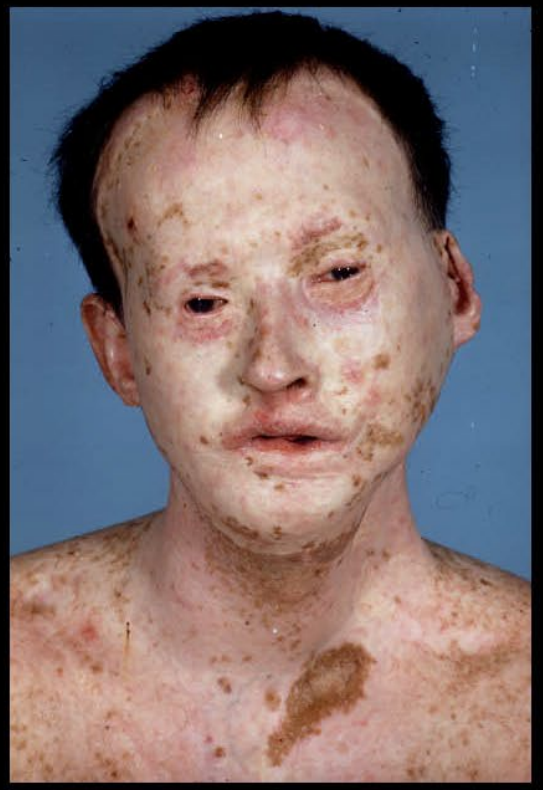


Modified from DiGiovanna and Kraemer JID 2012

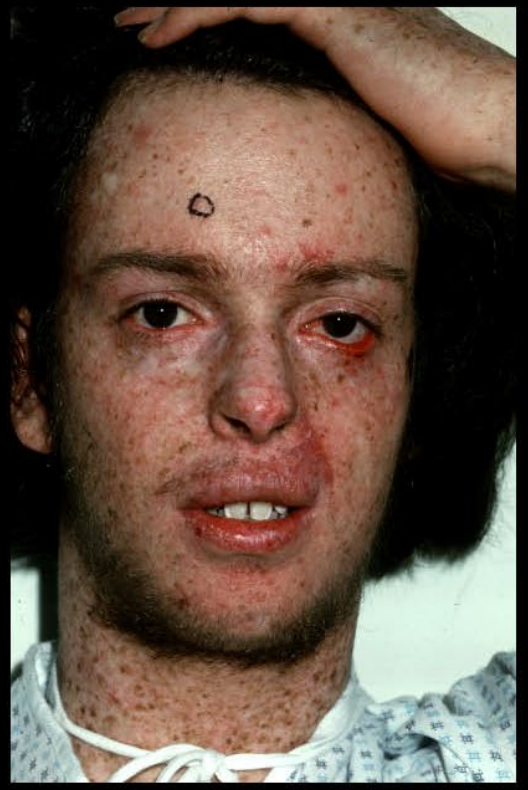
DNA REPAIR
IN INTERNAL CANCERS AND AGING



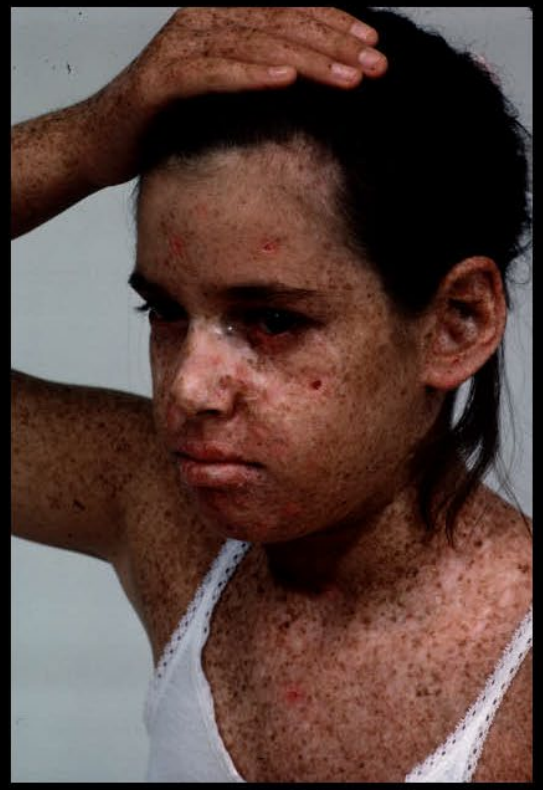
INTERNAL CANCERS IN XPC PATIENTS



XP3BE
LUNG
CANCER



XP23BE
ASTROCYTOMA
SPINAL CORD



XP24BE
GLIOMA
BRAIN

MIXED PHENOTYPE ACUTE LEUKEMIA
19 y/o XP-C patient from Morocco

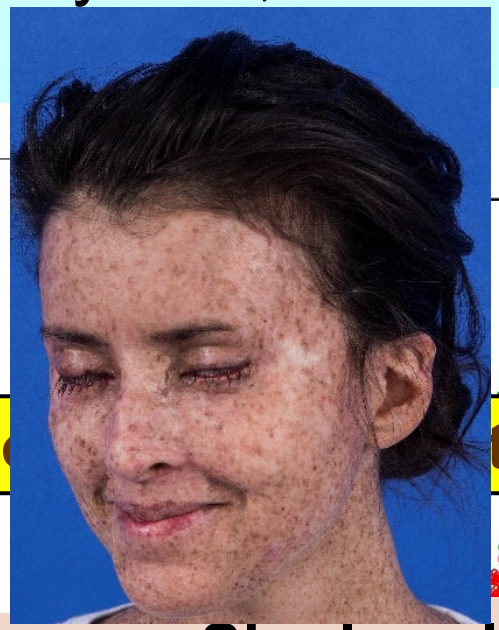
40+ skin cancers; multinodular thyroid; **North African *XPC* founder mutation**

18% blast cells: B/myeloid, T/B/myeloid, T/B blasts

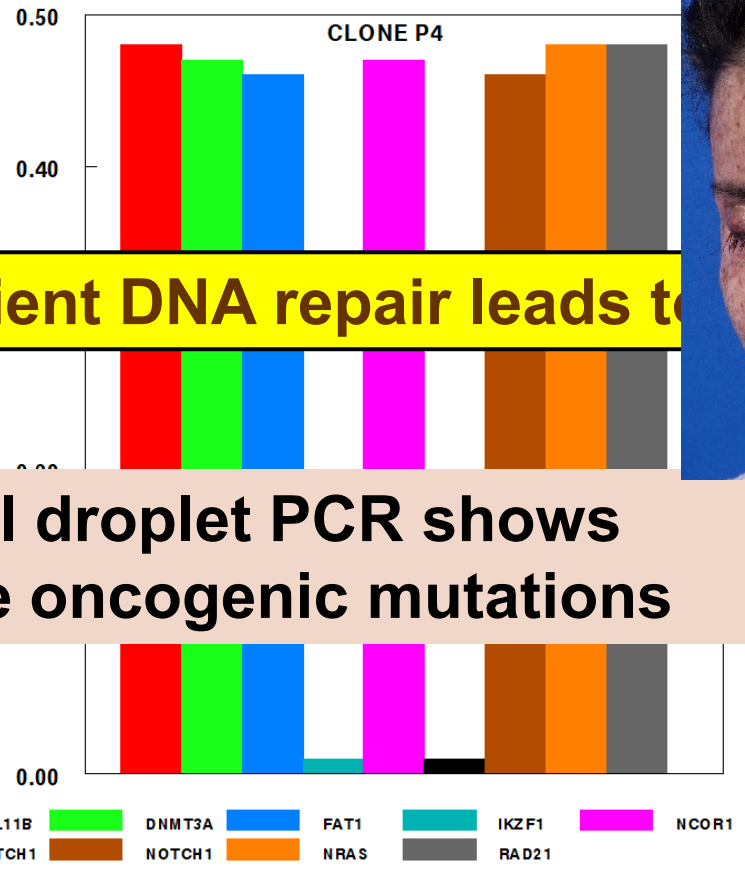
9 oncogenic mutations

Hematologists, NHLBI – Sawa Ito, Karolyn Oetjen

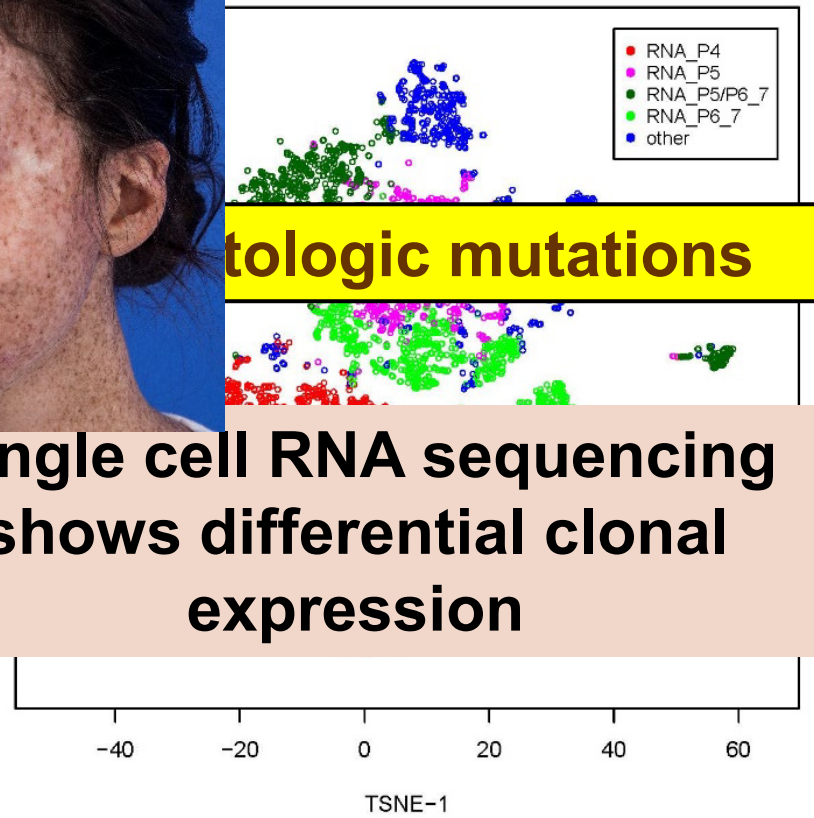
Sikandar Khan



Deficient DNA repair leads t tologic mutations



Digital droplet PCR shows Multiple oncogenic mutations



Single cell RNA sequencing shows differential clonal expression

Maxwell Lee

Howard Yang

Unpublished

HEMATOLOGIC NEOPLASMS IN XERODERMA PIGMENTOSUM

	Sex/Age	Complementation Group	Mutation	Outcome
MDS/AML	M/34 yr.	C	c.1643-1644delTG c.1103 1104delAA	Died 38 yr. - AML
MDS	M/18 yr.	C	c.622-2A>C	Died 20 yr. – complications s/p transplant
Diffuse Large B Cell Lymphoma	M/29 yr.	C	c.1643-1644delTG	Died 30 yr. – disease progression
MPAL	F/19 yr.	C	c.1643-1644delTG	Alive 20 yr. - chemotherapy

DNA repair plays a role in prevention of hematologic neoplasms

Mutations in Red are a common founder mutation.

MDS – myelodysplastic syndrome; AML – acute myeloid leukemia; MPAL – mixed phenotype acute leukemia

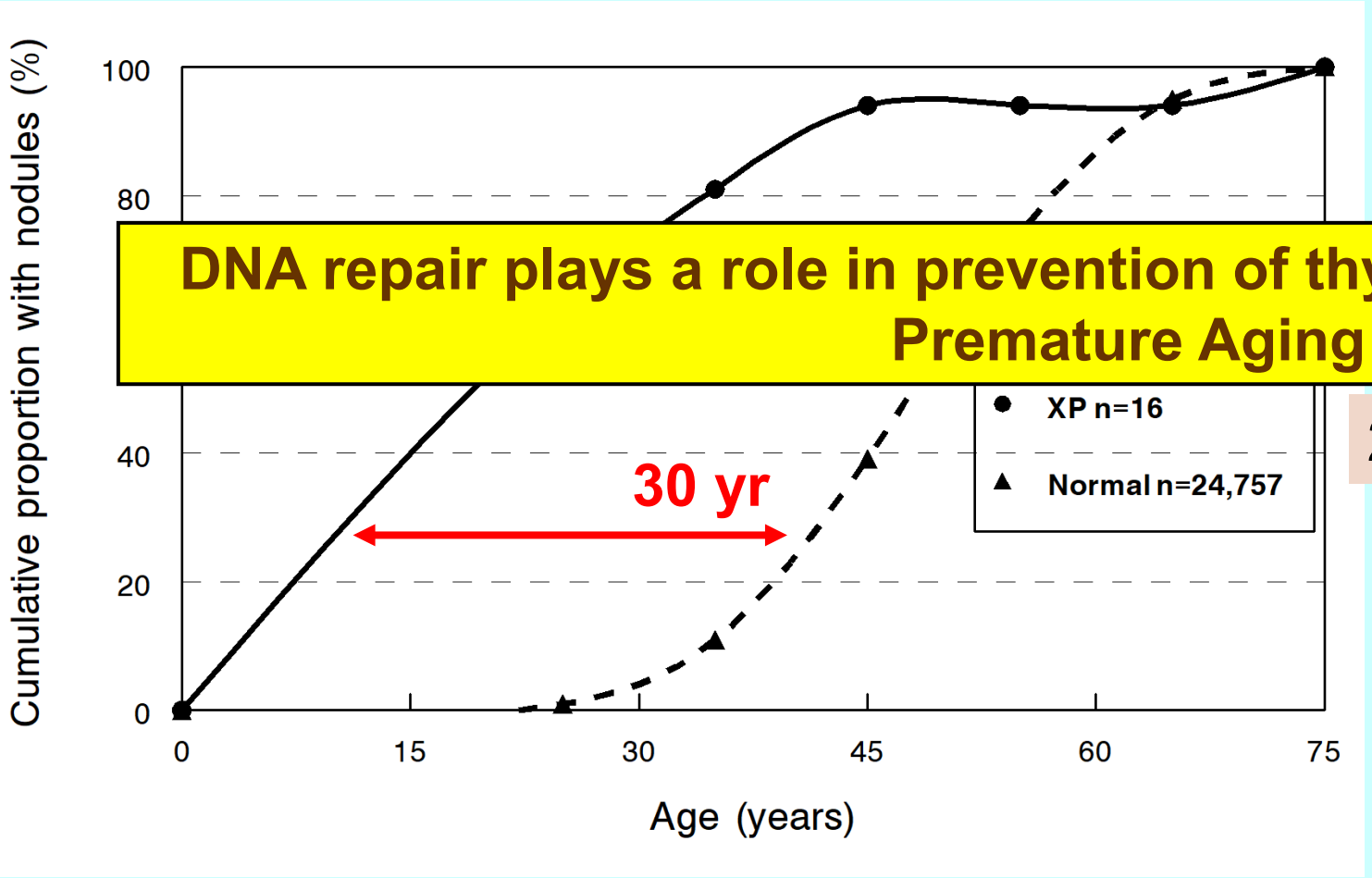
Question: Why is this **North African founder mutation** associated with hematologic neoplasms? - 13/161 (8%) of patients with **homozygous founder mutation** had MDS, AML or T-ALL -*Sarasin et al Blood (2019)*

Oetjen…**Kraemer,** DiGiovanna, Haematologica (2018)

EARLY AGE OF THYROID NODULES IN XERODERMA PIGMENTOSUM PATIENTS

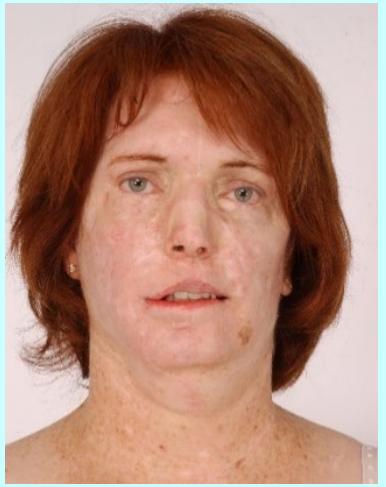
Samuel Kouatcheu

Radiology CC – Jamie Marko

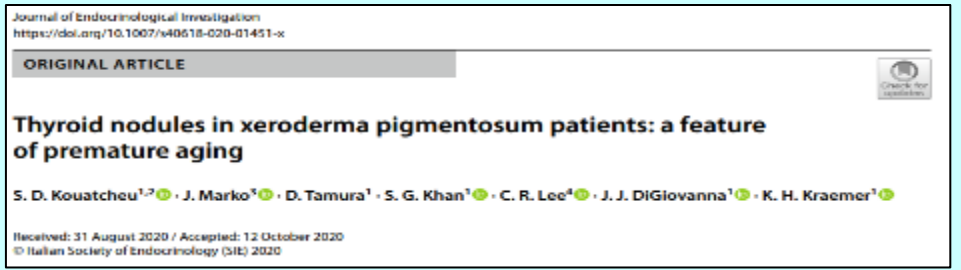


DNA repair plays a role in prevention of thyroid nodules and cancer
Premature Aging

2 XP patients had thyroid cancer



Thyroid cancer
TFG-NTRK1
fusion mutation



Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-020-01451-x

ORIGINAL ARTICLE

Thyroid nodules in xeroderma pigmentosum patients: a feature of premature aging

S. D. Kouatcheu[1,2] · J. Marko[3] · D. Tamura[1] · S. G. Khan[1] · C. R. Lee[4] · J. J. DiGiovanna[1] · K. H. Kraemer[1]

Received: 31 August 2020 / Accepted: 12 October 2020
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Nikolaev *et al.*
Orphanet Journal of Rare Diseases (2022) 17:104
https://doi.org/10.1186/s13023-022-02203-1

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Increased risk of internal tumors in DNA repair-deficient xeroderma pigmentosum patients: analysis of four international cohorts

Sergey Nikolaev[1*], Andrey A. Yurchenko[1] and Alain Sarasin[2*]

2022

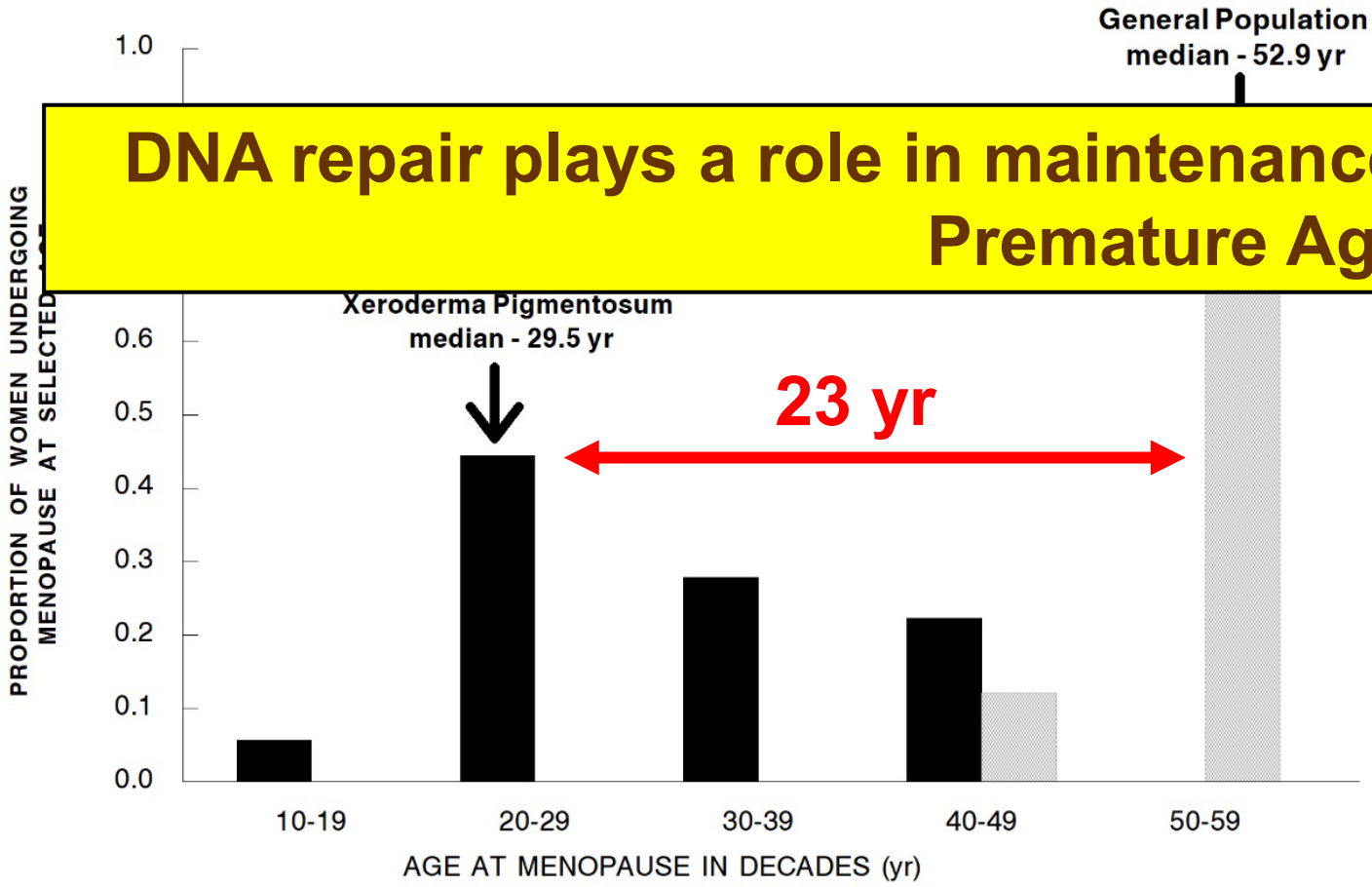
- **34 - fold increased risk for all internal tumors**
- **CNS tumors, hematologic cancer most commonly seen**

PREMATURE MENOPAUSE IN WOMEN WITH XERODERMA PIGMENTOSUM

Deborah Tamura

Ob-Gyn NHGRI – Melissa Merideth

DNA repair plays a role in maintenance of normal ovarian function
Premature Aging



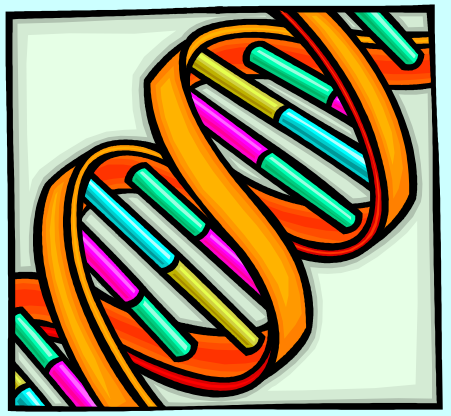
women 18 years or older

9 women had documented primary ovarian insufficiency

2 women had atrophic ovaries on autopsy

Merideth, Tamura… **Kraemer**
Obstetr Gynecology (2019)

TRICHOTHIODYSTROPHY (TTD)
DNA REPAIR/ TRANSCRIPTION GENES



TRICHOTHIODYSTROPHY: CLINICAL FEATURES

Alan Zhou

MATERNAL PREGNANCY ABNORMALITIES

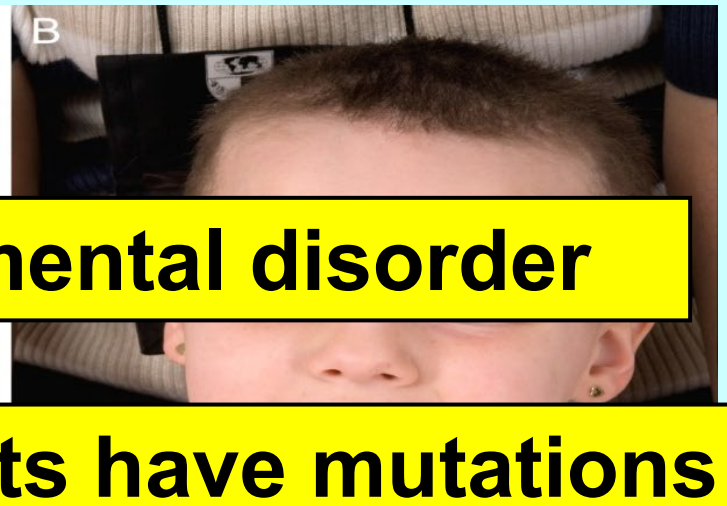
C

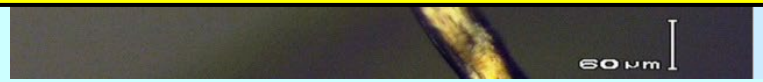
MEMBRANE AT BIRTH

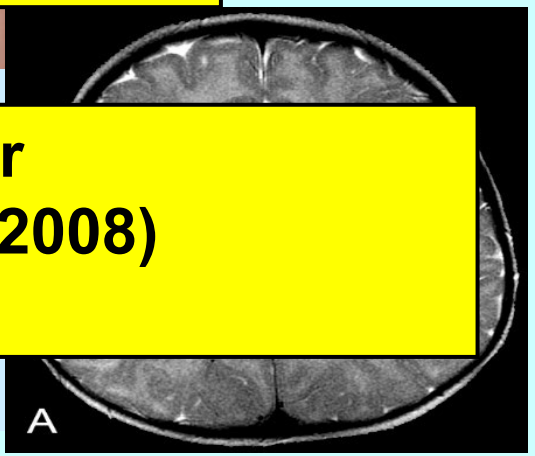
TIGER-TAIL BANDING (POLARIZED M

TI

MICROSCOPY)







TTD is primarily a developmental disorder

TTD patients have mutations in XP genes (*XPD*, *XPB*) but no increase in cancers

20-fold increased risk of death under age 10 yr
(Faghri, Tamura, Kraemer, DiGiovanna J Med Gen 2008)
9 of 36 TTD CHILDREN in our study DIED!

SHORT, SPARCE BRITTLE SCALP AND EYEBROW HAIR
LONG YELASHES
4 Y/O

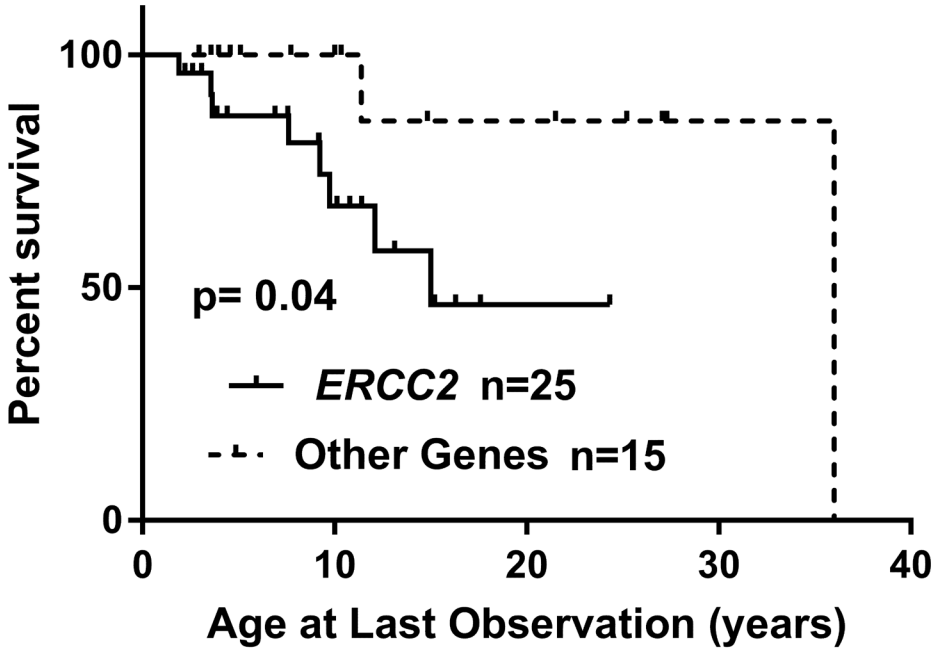
XPD

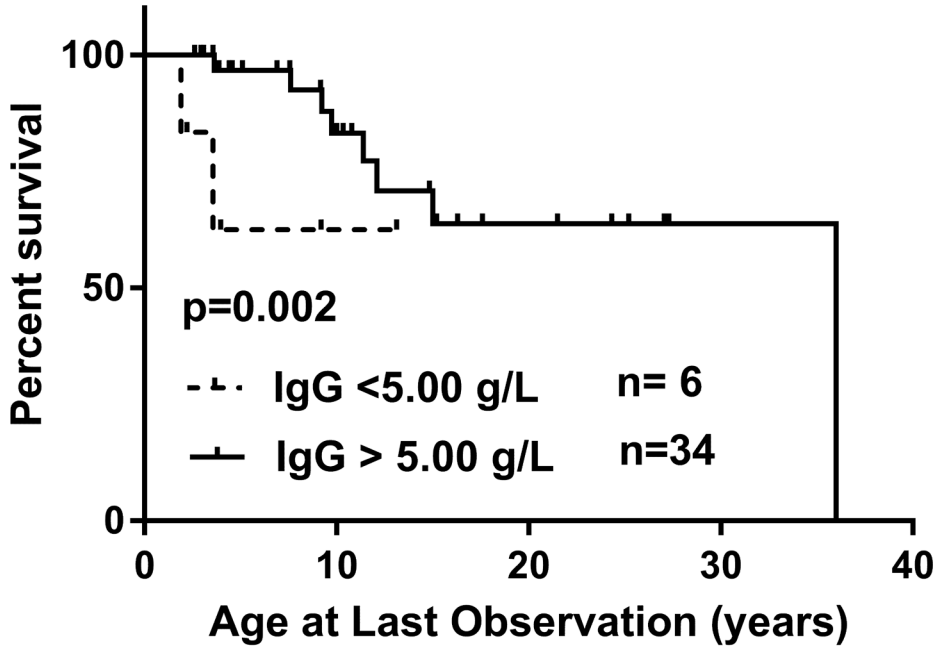
Zhou … Kraemer JAAD 2010

DECREASED SURVIVAL OF TTD PATIENTS WITH *ERCC2/XPD* MUTATIONS OR LOW IgG

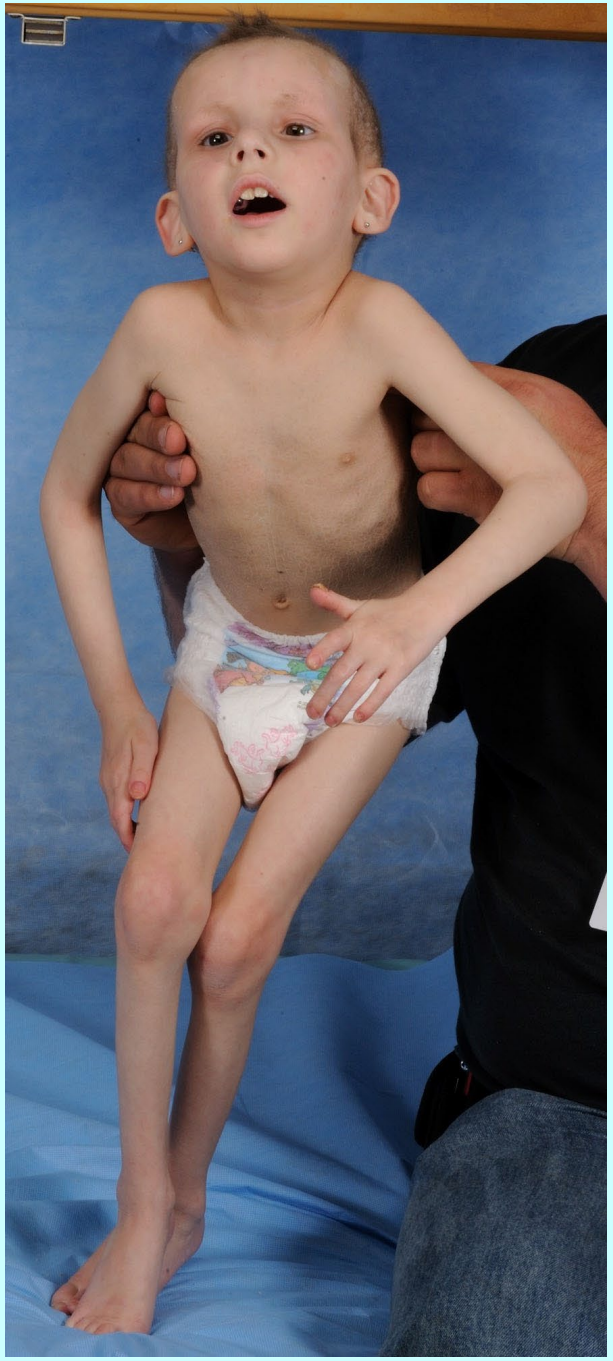
Reduced survival of trichothiodystrophy patients with *ERCC2* (*XPD*) mutations or immune deficiency

A.





Randall, Kraemer et al Br J Hematol 2019



Received: 6 May 2022 | Revised: 25 July 2022 | Accepted: 11 August 2022

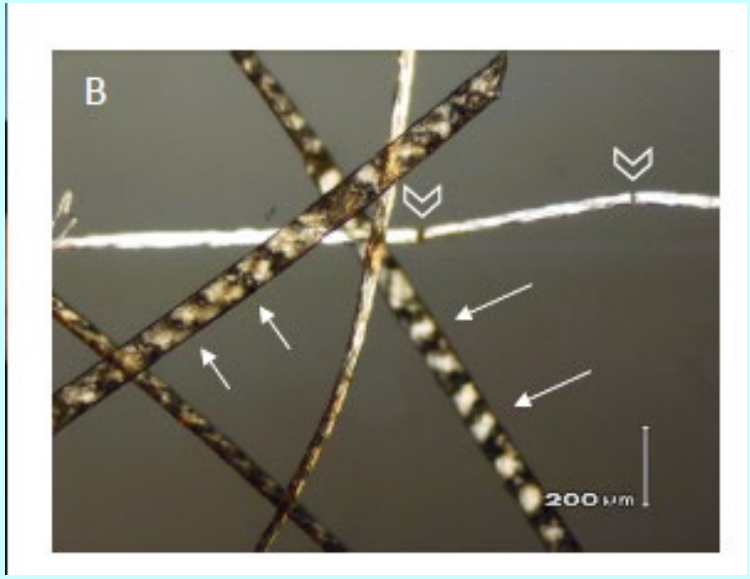
DOI: 10.1002/ajmg.a.62962

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

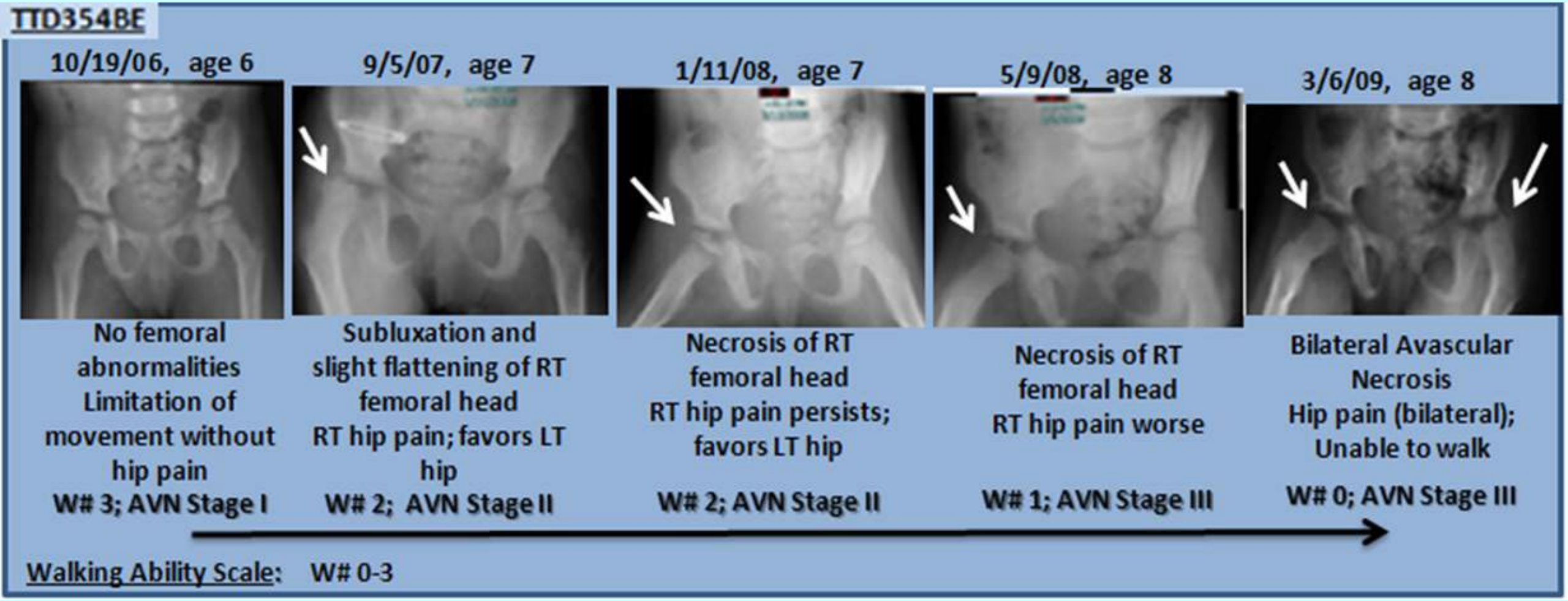
Debilitating hip degeneration in trichothiodystrophy: Association with *ERCC2/XPD* mutations, osteosclerosis, osteopenia, coxa valga, contractures, and osteonecrosis

John J. DiGiovanna[1] | Grant Randall[1,2] | Alexandra Edelman[1] | Rina Allawh[1] | Michael Xiong[1] | Deborah Tamura[1] | Sikandar G. Khan[1] | Elizabeth R. H. Rizza[1] | James C. Reynolds[3] | Scott M. Paul[4] | Suvimol C. Hill[5] | Kenneth H. Kraemer[1]

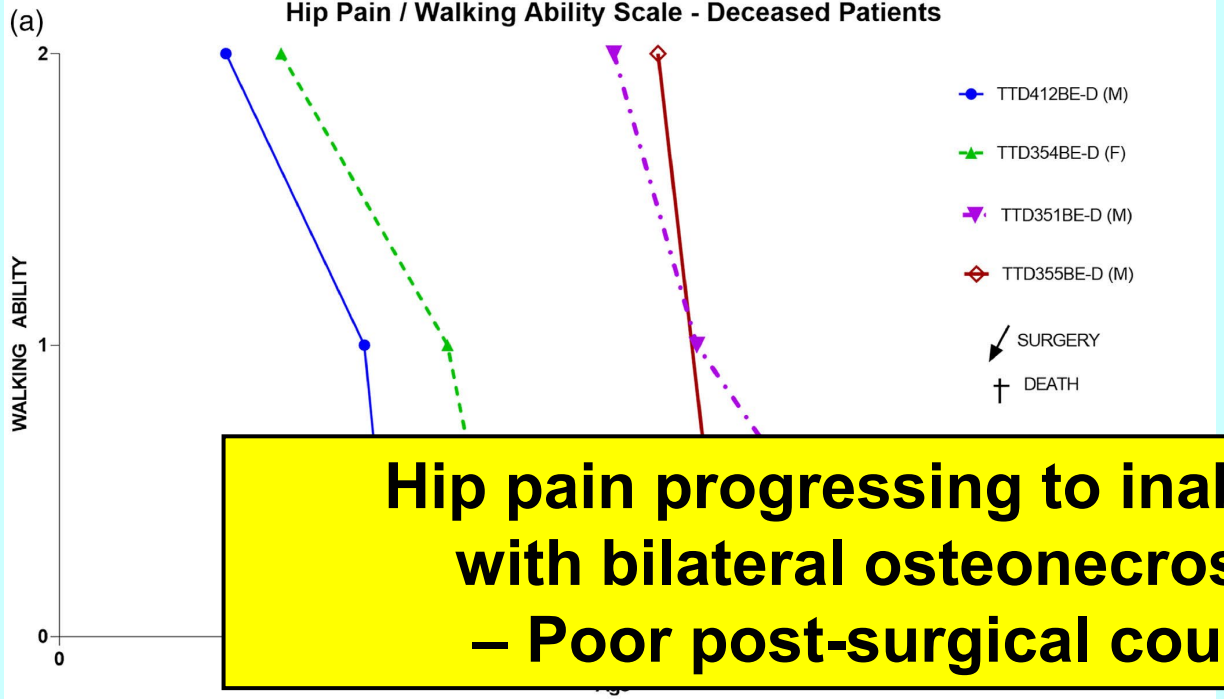


John DiGiovanna M.D.
Senior Research Physician

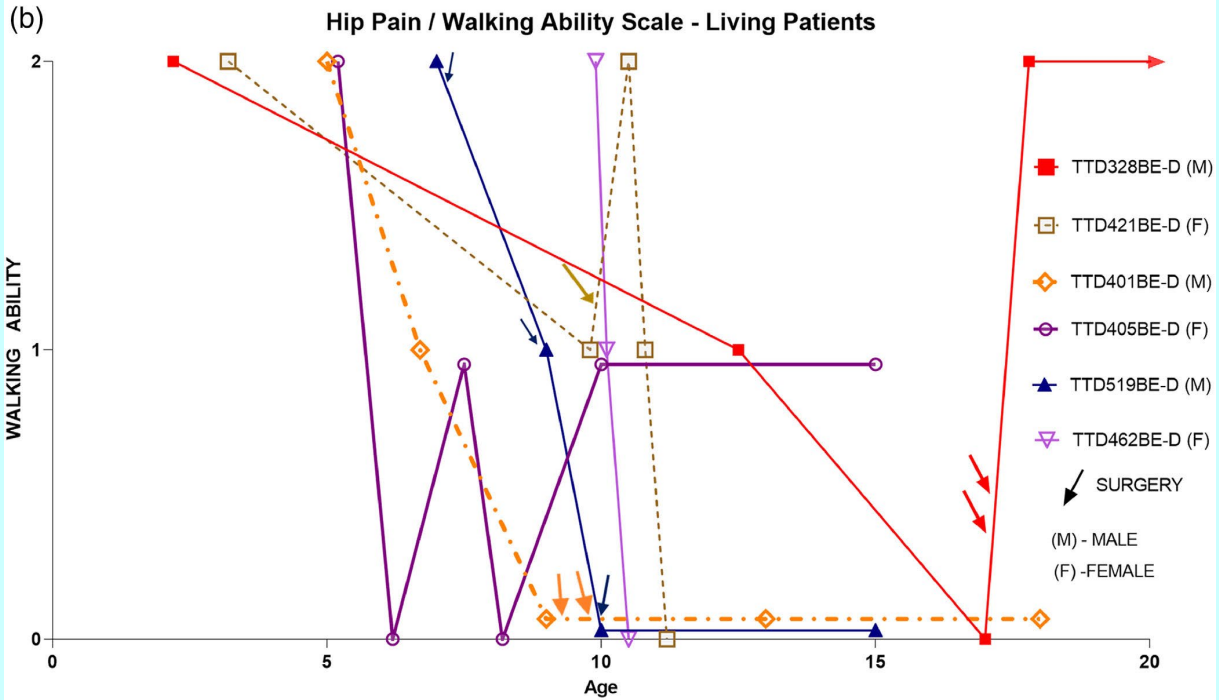
PROGRESSIVE AVASCULAR NECROSIS OF HIPS IN YOUNG TRICHOTHIODYSTROPHY PATIENT



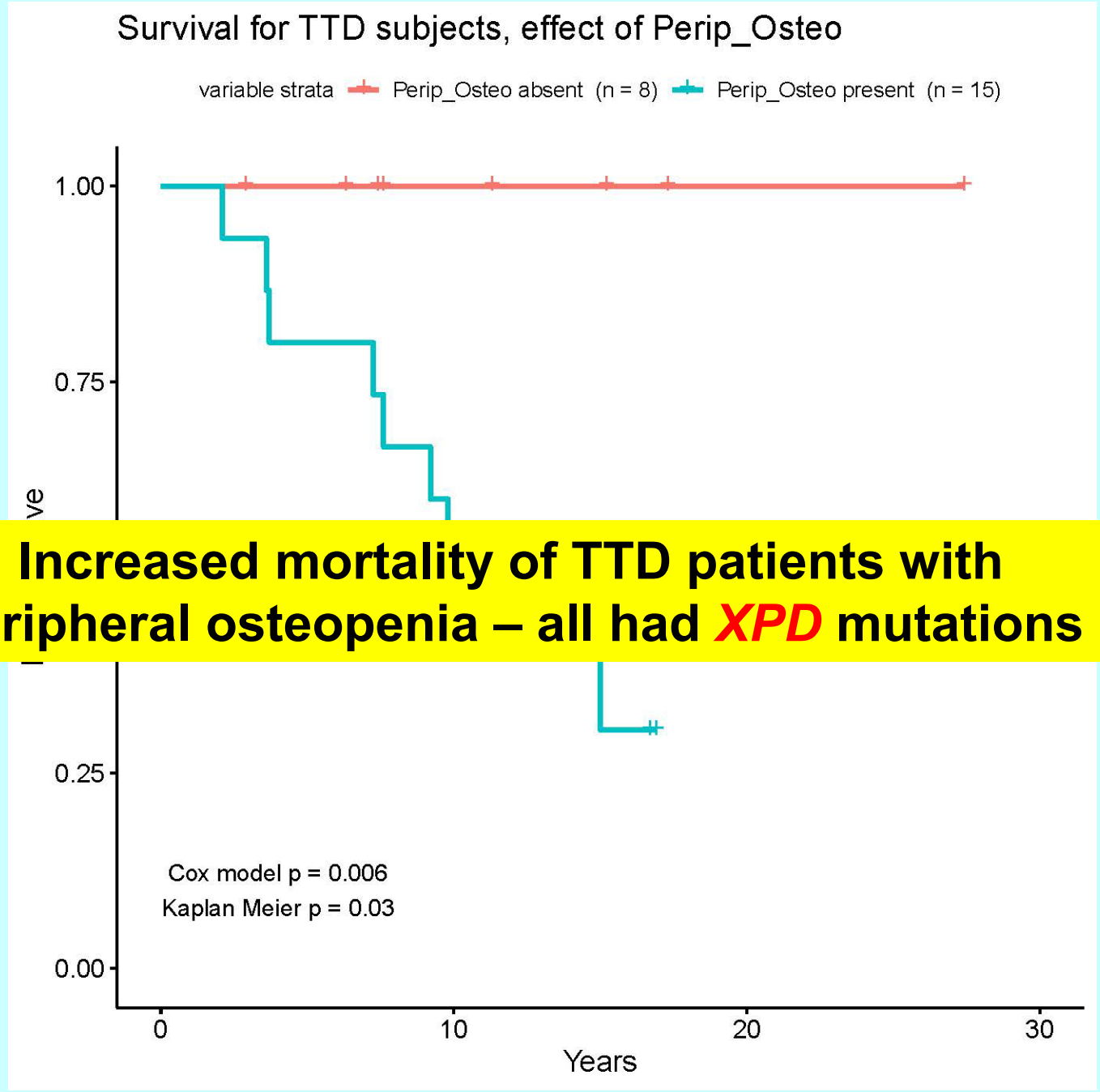
DiGiovanna et al Am J Med Gen 2022



Hip pain progressing to inability to walk with bilateral osteonecrosis of hips – Poor post-surgical course - *XPD*



DiGiovanna et al
Am J Med Gen 2022



Increased mortality of TTD patients with Peripheral osteopenia – all had *XPD* mutations

PRENATAL DIAGNOSIS
Prenat Diagn (2011)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/pd.2829

High-risk pregnancy and neonatal complications in the DNA repair and transcription disorder trichothiodystrophy: report of 27 affected pregnancies

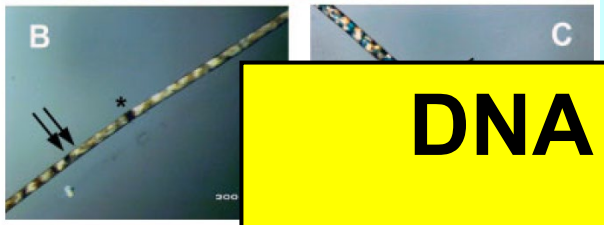
Deborah Tamura[1], Melissa Meredeth[2,3], John J. DiGiovanna[1], Xiaolong Zhou[1,4], Margaret A. Tucker[5]
Alisa M. Goldstei
Roxana Moslehi[7]

Deborah Tamura

81% of mothers with *XPD* mutations carrying a TTD fetus have pregnancy complications

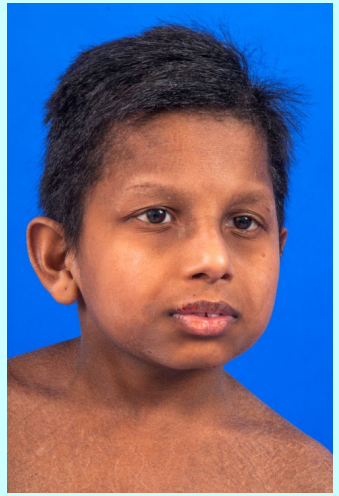
Pre-term delivery
Pre-eclampsia
Low birth weight

No mothers with *XPD* mutations carrying a XP fetus have pregnancy complications

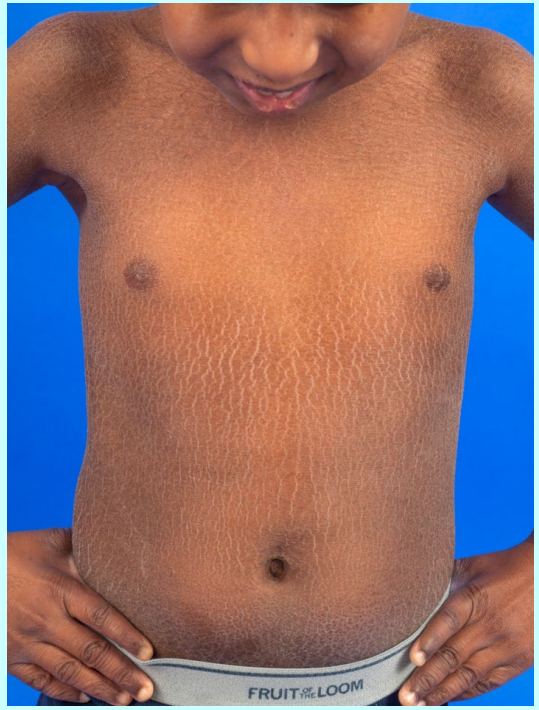


DNA repair/transcription genes play a role in normal fetal development

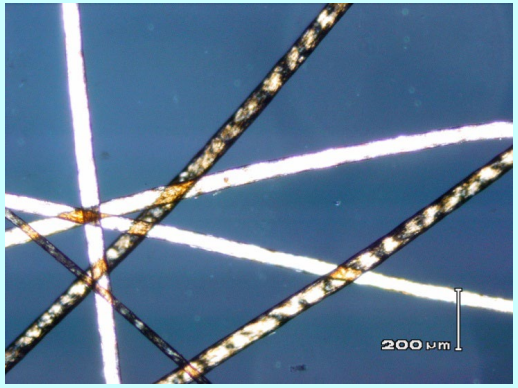
TTD PATIENT: 10 Y/O INDIAN MALE



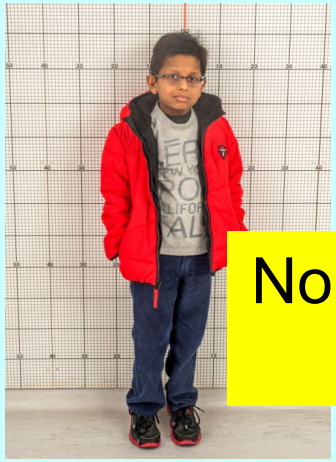
Brittle hair, sparse eyebrows
Mild nystagmus, micrognathia



Ichthyosis involving the trunk, back, scalp and legs



Tiger-tail banding under polarized light microscopy

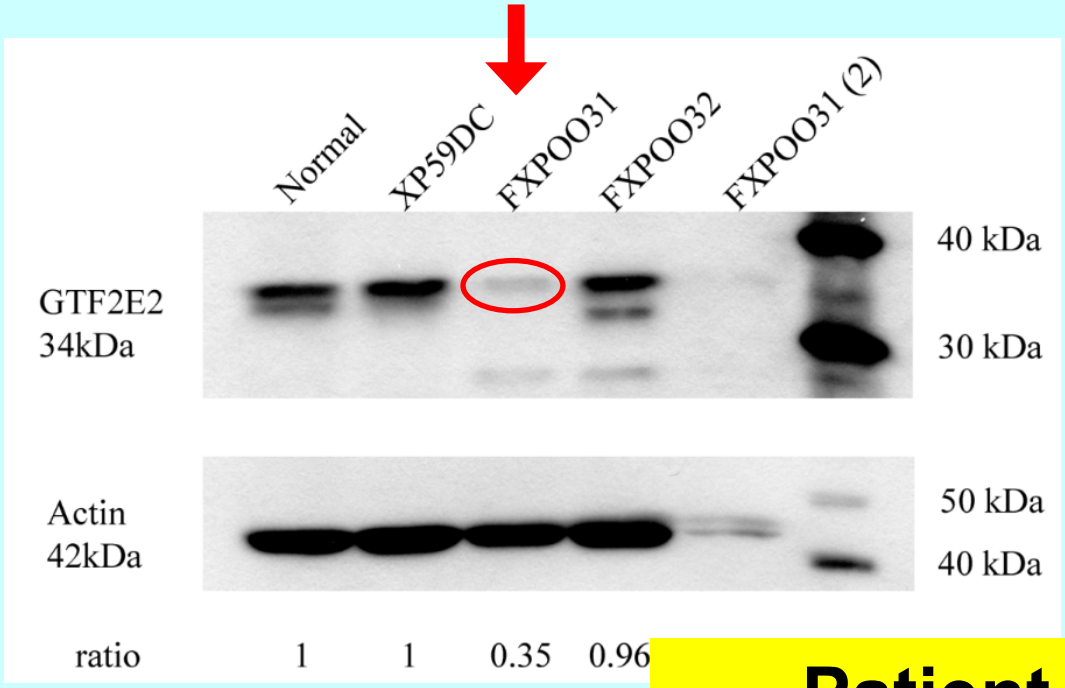


Microcephaly, Short stature

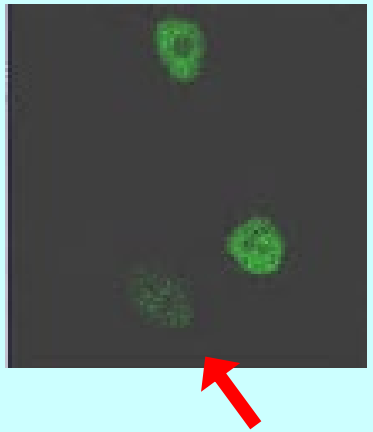
No mutations in known TTD genes
(*XPB*, *XPD*, *TTD-A*, *TTDN1*)

Hair shaft abnormalities
(fracturing; irregular contour)

GTF2E2 MUTATION



- Reduced TFIIE protein
- Normal post-UV cell survival
- Normal level of XPB, XPD
- Normal post-UV localization of NER proteins



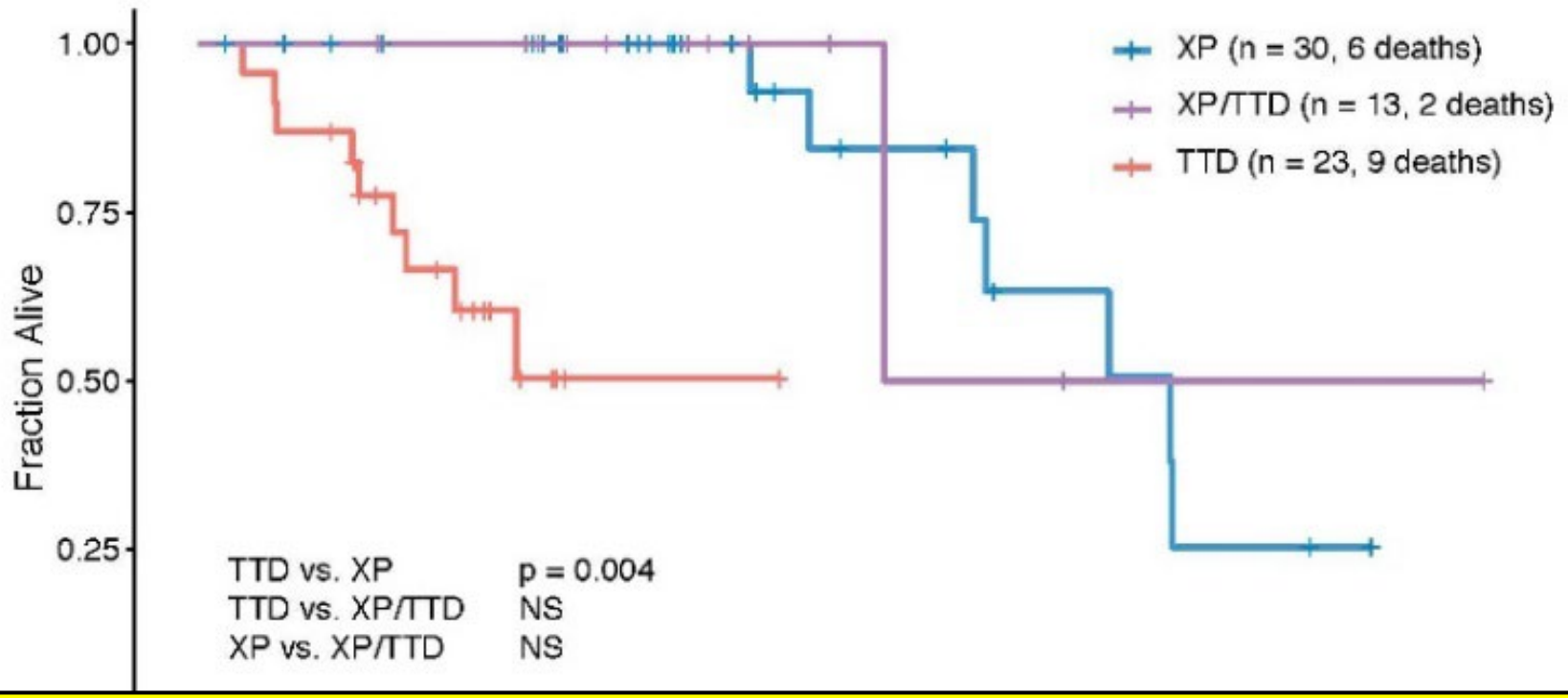
GTF2E2

Patient has reduced GTF2E2 protein but normal nucleotide excision repair
"Pure" transcription defect

Kuschal et al Am J Human Genetics 2016

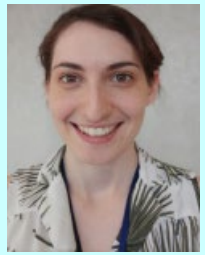
DEEP PHENOTYPING with HIERARCHICAL CLUSTERING of CLINICAL FEATURES ASSISTS IN PROGNOSIS

66 patients with *ERCC2 (XPD)* mutations:
30 XP, 13 XP/TTD, 23 TTD



TTD patients have a greater reduction in survival than the XP or XP/TTD patients

***TTDN1* patients have distinct phenotype JID 2014**

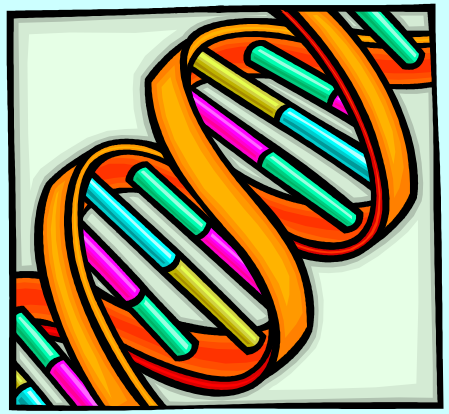

Elizabeth Heller


Jennifer Pugh


George Nelson

Unpublished

DNA REPAIR GENES IN GENERAL POPULATION MOLECULAR EPIDEMIOLOGY



Available online at www.sciencedirect.com
ScienceDirect
Mutation Research 601 (2006) 171–178
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Heterozygous individuals bearing a founder mutation in the *XPA* DNA repair gene comprise nearly 1% of the Japanese population

Yuko Hirai [a,*], Yoshiaki Kodama [a], Shin-Ichi Moriwaki [b], Asao Noda [a], Harry M. Cullings [c], Donald G. MacPhee [d], Kazunori Kodama [e], Kiyohiko Mabuchi [f], Kenneth H. Kraemer [g], Charles E. Land [f], Nori Nakamura [a]

1 million carriers of the *XPA* mutation in Japan

[c] Department of Statistics, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan
[d] Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan

Cancer risk of *XPA* heterozygotes is not known

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Available online 14 August 2006

USE OF BIG DATA TO ESTIMATE PREVALENCE OF DEFECTIVE DNA REPAIR VARIANTS IN THE US POPULATION

Question: Do databases of exome sequences reliably correlate with the prevalence of individuals with defective DNA repair?

Table 2. Higher Frequency of *XPF* (*ERCC4*) and *XPC* Mutations in Genetic Databases Compared With Phenotypic XP Observed in the United States

Complementation Group (Gene)	Mutation Associated With XP	Total No. of Alleles Sequenced	No. of Individuals	No. of Alleles	% of Alleles Reported in Database (q)	Estimated % of Homozygous Affected Individuals (q^2)[a]	Total No. of Genetic Homozygotes Reported in Database	Total No. of Genetic Homozygotes Estimated in Database[a]	rs No.[b]
gnomAD									
XPF (*ERCC4*)	p.P379S	276 560	138 280	1122	0.41	1.65×10^{-5}	4	2.28	rs1799802
XPF (*ERCC4*)	p.R799W	277 034	138 517	124	0.04	2.00×10^{-7}	0	0.03	rs121913049
XPC	p.P334H	274 914	137 457	838	0.30	9.29×10^{-6}	7	1.28	rs74737358

Jennifer Pugh

Large exome databases revealed high frequencies of 2 DNA repair gene mutations associated with xeroderma pigmentosum

Pugh … **Kraemer** JAMA Derm 2018

PREDICTED FREQUENCY OF XP IN THE UNITED STATES

US estimations									
XPF (*ERCC4*)	p.P379S	NA	323 100 000[d]	NA	0.41[e]	1.65×10^{-5}	3[f]	5298[g]	rs1799802
XPF (*ERCC4*)	p.R799W	NA	323 100 000[d]	NA	0.04[e]	2.00×10^{-7}	11[f]	66[g]	rs121913049
XPC	p.P334H	NA	323 100 000[d]	NA	0.30[e]	9.29×10^{-6}	1[f]	3002[g]	rs74737358
65 XP mutations[h]		NA	NA	NA	1.13[e]	2.81×10^{-5}	300 (US only)[f]	9007[g]	NA

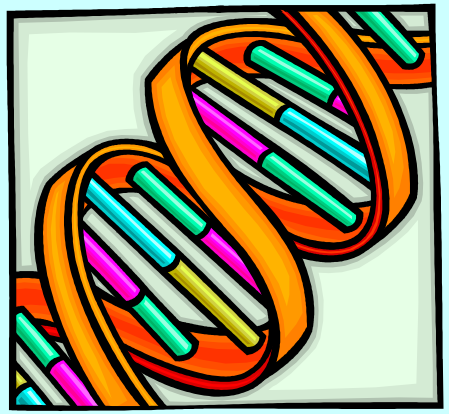
These frequencies estimate the presence of more than 8,000 people with xeroderma pigmentosum in the US who are homozygous for these mutations, yet only 4 individuals were clinically identified.

CONCLUSION: Discrepancy between large number of XP genotypes in database and known number of XP patients.

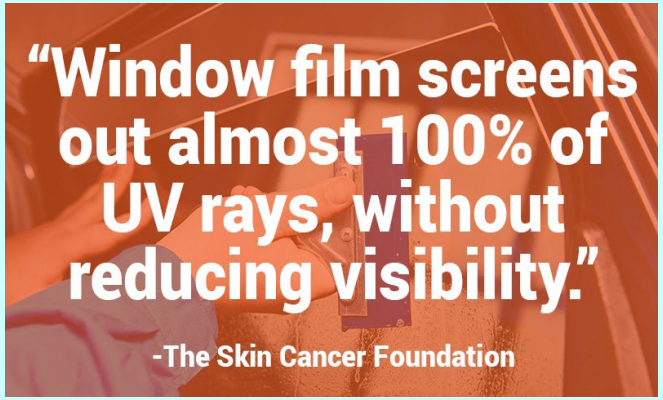
HYPOTHESIS: Unsuspected mutations in known skin cancer genes may be responsible for some of the high frequency of skin cancers in the general population.

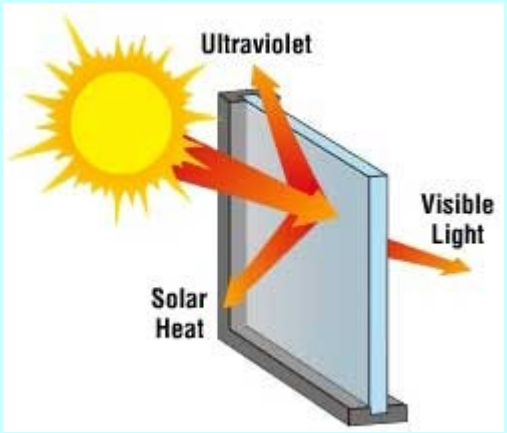
Pugh … **Kraemer** JAMA Derm 2018

MANAGEMENT OF PATIENTS WITH XERODERMA PIGMENTOSUM



XERODERMA PIGMENTOSUM
SUN PROTECTION

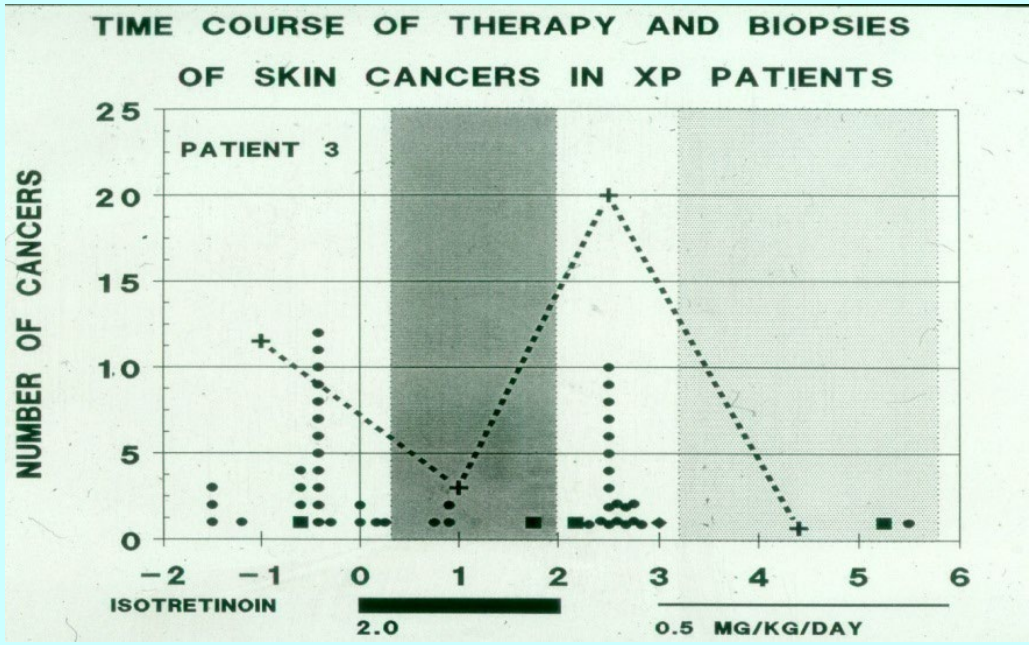




ORAL ISOTRETINOIN PREVENTS NEW SKIN CANCERS IN XERODERMA PIGMENTOSUM

Table 1. Number of Skin Cancers in Patients with Xeroderma Pigmentosum before, during, and after Therapy with Oral Isotretinoin (2 mg per Kilogram per Day).

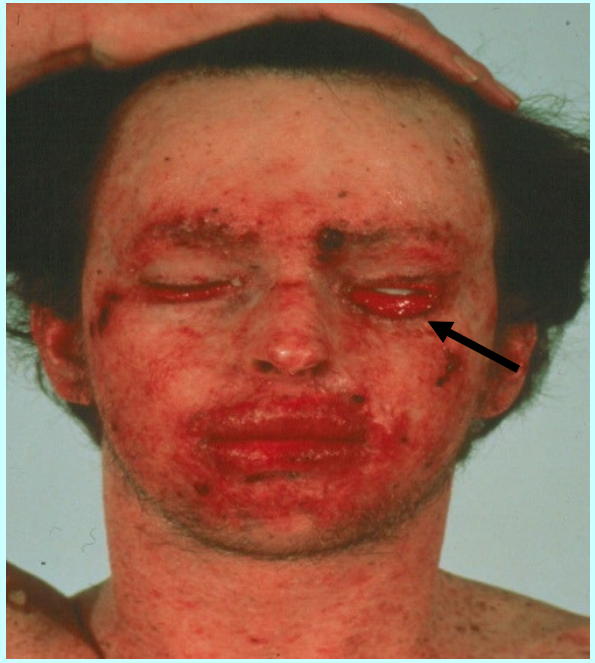
Patient	Age/Sex	Before Treatment* (2 Yr)	During Treatment* (2 Yr)	After Treatment† (12–14 Mo)
		number (number per year)		
1	19/F	43 (21.5)	3 (1.5)	18 (18.0)
2	12/F	37 (18.5)	4 (2.0)	29 (38.7)‡
3	17/M	23 (11.5)	6 (3.0)	20 (20.0)
4	39/M	10 (5.0)	3 (1.5)	4 (3.4)
5	10/M	8 (4.0)	9 (4.5)	10 (10.0)



Oral retinoid effective in PREVENTION of new cancers in XP patients

Kraemer et al NEJM 315: 1615 (1988)

SIDE EFFECTS OF ORAL ISOTRETINOIN FOR XERODERMA PIGMENTOSUM



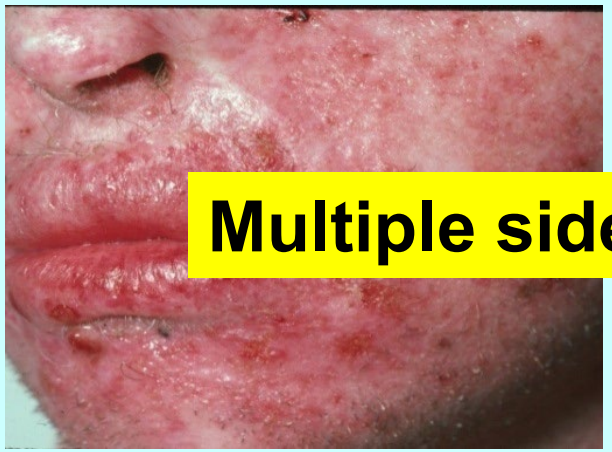
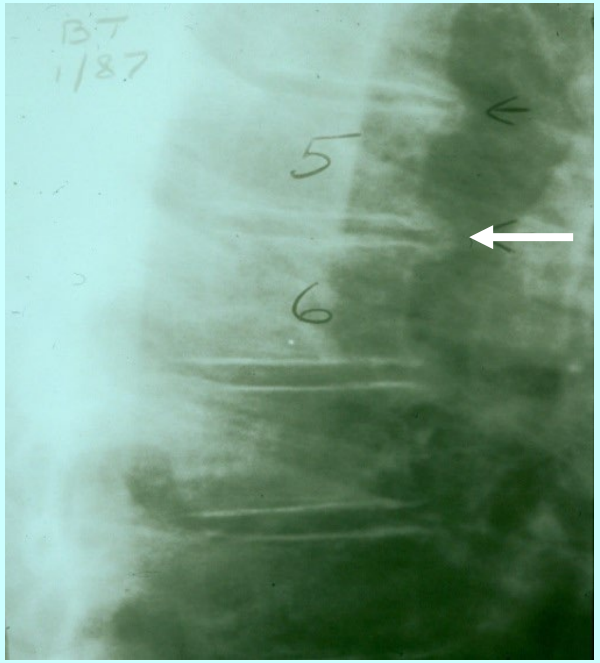


Table 2. Frequency of Side Effects Observed in Seven Patients with Xeroderma Pigmentosum during Treatment with Oral Isotretinoin (2 mg per Kilogram per Day).

Side Effect	No. of Patients Affected
Dry skin	7
Cheilitis	7
Blepharitis or Conjunctivitis	7
Lightening or disappearance of freckles	6
Increased serum triglycerides	6
Abnormal liver-function tests	4
Arthralgias	4
Staphylococcal infection (perioral)	3
Multiple pyogenic granulomas	2
Skeletal toxicity	2



Multiple side effects by use of oral retinoid in XP patients

Kraemer et al
NEJM 315:1615 (1988)

LONG TERM SUN PROTECTION IN XERODERMA PIGMENTOSUM

XP34BE 5 yr

XP35BE 1 yr

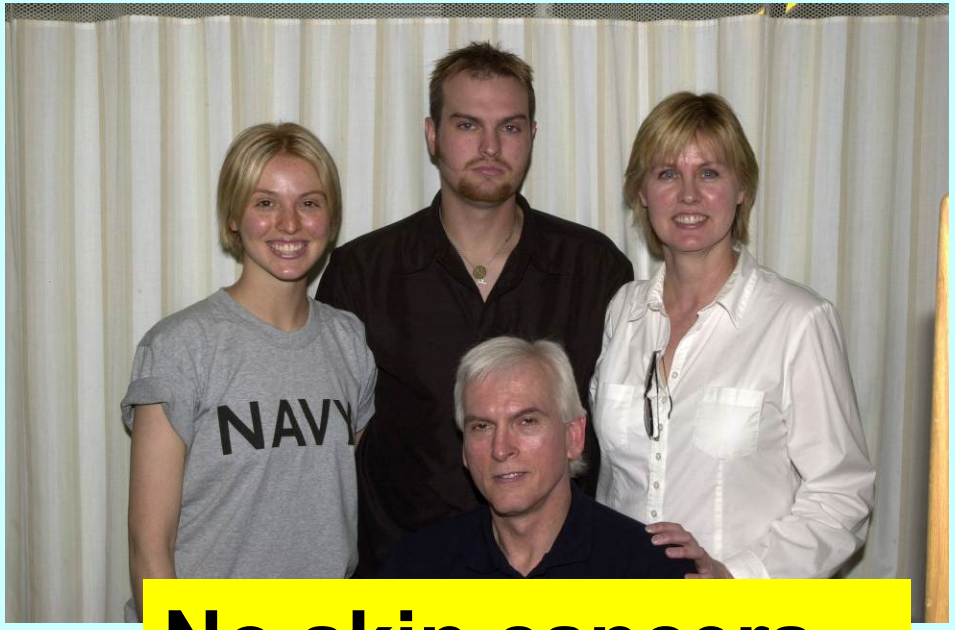
Living in Denver, CO

XPD family

Moved to Seattle, WA

XP35BE 19 yr

XP34BE 23 yr



No skin cancers

Long Time Partners

OUR PATIENTS AND THEIR FAMILIES

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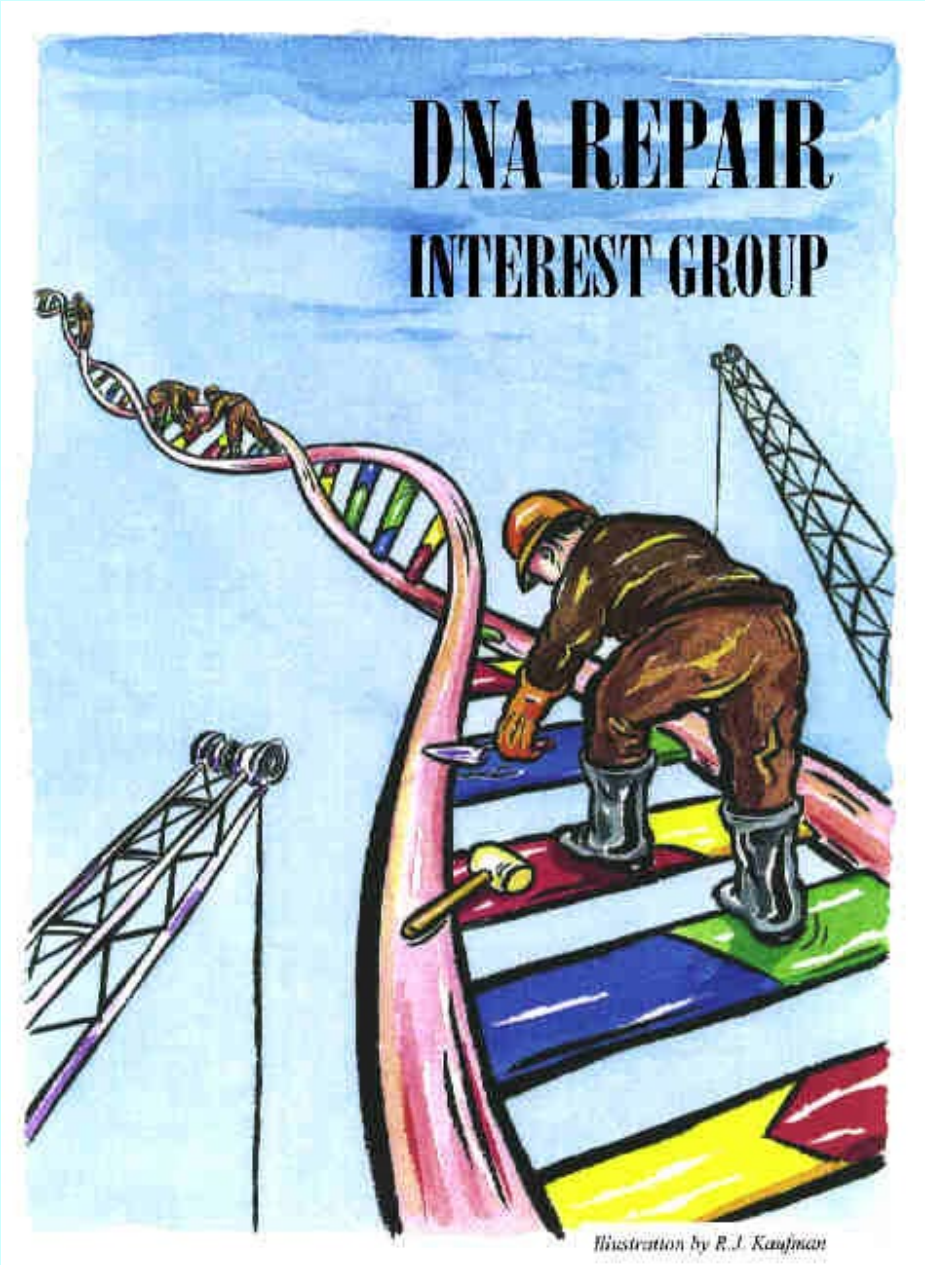
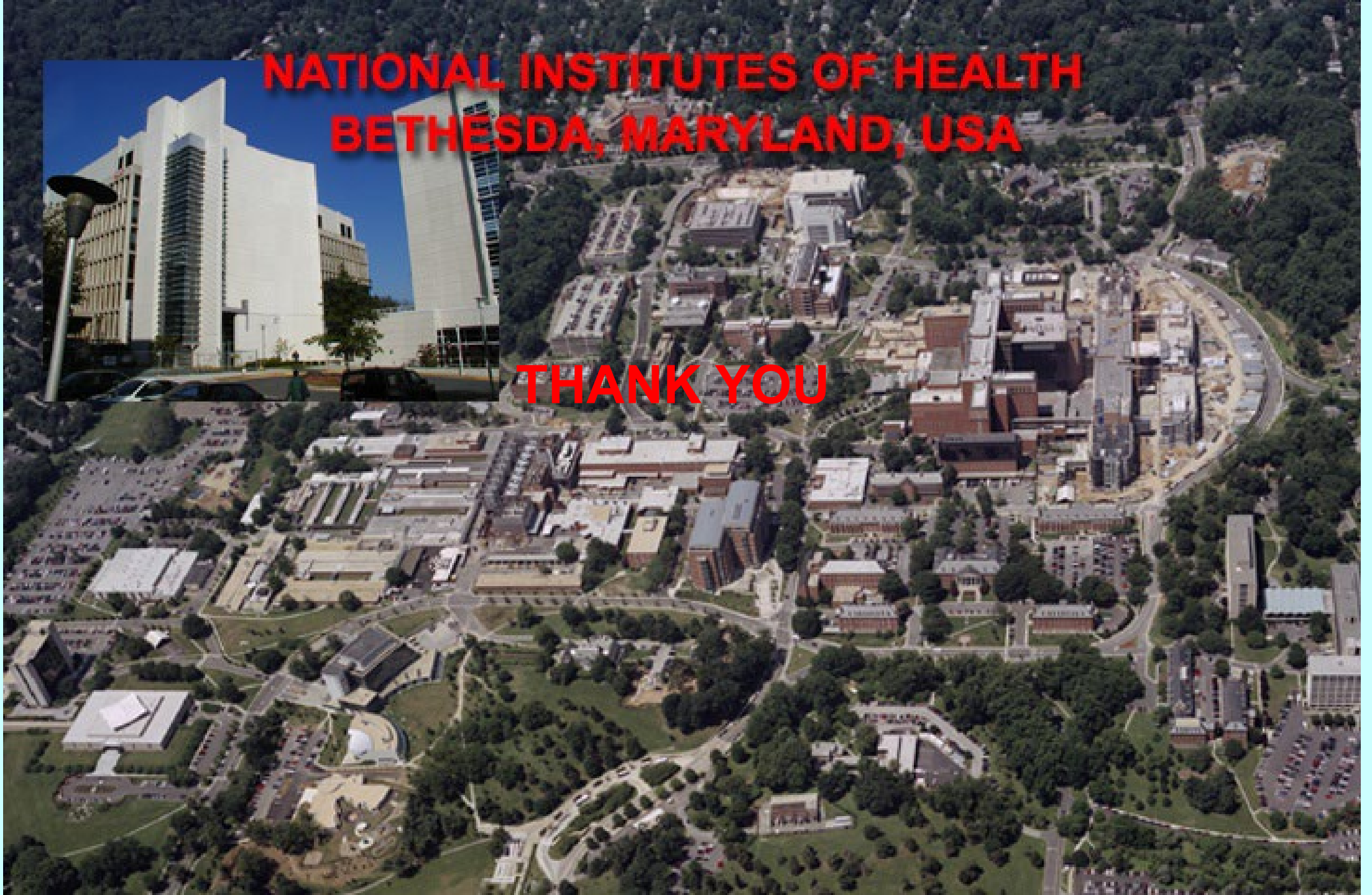
Deborah Tamura	Grant Randall	Jennifer Pugh		



- Co-chair with Dr. V. Bohr, NIA.
- Established 1985
- Monthly videoconferences
- 8 linked sites across US (now unlimited virtual lectures)
- >250 lectures archived at http://videocast.nih.gov
- e-mail list: >1200 subscribers worldwide
- kraemerk@nih.gov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THANK YOU