1st International XP Medical Conference & Camp

London 9-12 February 2018

CONFERENCE PRESENTATIONS

XP FAMILY SUPPORT GROUP

United States of America

Board of Directors

- Todd Feltner – President
- Miranda Murphy- Secretary
- Sarah Madden – Treasurer
- Jennifer Feltner
- Alan Jakovac
- Rossi Byrnes
- Kyle Madden
- Cathy Hancock
- Kittie Tenney

How We Got Started

- Founded in 2005
- Families banded together to form non-profit

Accomplishments

- Window Film Legislation
- XP Documentary – Hidden from Light
- Talk on Capital Hill
- Media Attention
- Guatemala
- AAD/XP Task Force
- Global Skin Disease

Services We Provide

- New Patient Package
- UV Light Meter
- UV Window Film for Home/Car
- Hat Pattern/Video
- XP Information

Fundraising

- Crab Feed
- Krispy Kreme Donut Sales
- Walk/Fun Run
- Golf Tournaments
- Vacation Raffle
- Technology Raffle
- Car/Motorcycle Raffle
- Gun Raffle
- Restaurant Fundraisers
- Steam Boat Challenge
- Toast for Hope
- Glow Golf Balls/Helicopter

2018 Medical Conference

- Wichita, KS
- November 8 – 11, 2018
- Medical Talks
- Firefly Kids Camp
- Family Activities

Collaboration with world wide XP groups

ENFANTS DE LA LUNE
XP Support Group

- Created in October 2000 by Bernard and Françoise Séris
- 400 members and donors
- Development of UV protection
- 22 years of practice of the UV protection : Vincent and Thomas Séris have not developed cancers since the implementation of UV protection ➔ FUTURE
- XP families follow up : listening and replying to questions and various demands

Enfants de la Lune
Association pour le Xeroderma Pigmentosum

3 rue Corneille
01200 Bellegarde sur Valserine
0033 4 57 05 13 61

Website : www.enfantsdelalune.org

Facebook : www.facebook.com/EnfantsDelalune.org

Répartition géographiques des malades

- **91 patients**
- **65 families**
- **403 members**
- **3 to 6 new diagnosed children per year**

Source : Enfants de la lune
Janvier 2018

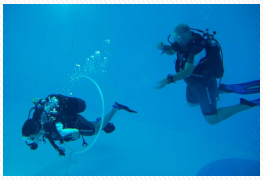
XP Family Support Group Enfants de la lune

Target	Result
Breaking social isolation	Multiple grouping of patients with their family during the year
Implementation of daily UV protection.	Significant decrease of the disease evolution
Find solutions that combine protection and quality of life.	Official recognition through a National Diagnostic and Care Protocol in 2007 related to XP
Obtain from the public authorities a real social care of this disease (payback, schooling, ...).	Social security (derogation package (1300 € / year / patient)) - Ministerial decree of 2 October 2009. / Schooling without risk of UV exposure
Regular R&D in order to relieve everyday life	Development of a transparent ventilated anti-UV mask. Provide all equipment of UV protection (6000€ per family with one XP)
Research supporting	2 labs (INSERM Bordeaux and IGR Paris)

What we do

- Organize annual camps
- Finance the protection
- Obtain from the public authorities a real social care
- Regular R&D
- Research supporting

Support by Doctors and researchers



Mask project

» ENFANTS DE LA LUNE XP Support Group

- Fundraising
  - > Other association, club services (Rotary and Lion's club)
    - + Concerts
    - + First filght
  - > Fondation
  - > Annual party
  - > Cake sale on markets
  - > Goodies

Mask project

From DIY to industrial and certified CE protection.

Project plan : from the idea to the prototype

13

August 2010

SPECIFICATIONS

April 2011

Test of some proof of concept

Application

September 2012

April 2012

Creation of a prototype

Project team

Project management

Contributors

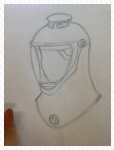
Financial Partners

Project management

Supervisor : Emilie Giret

Project manager : Florent Hyafil

Collaboration with Engineers from CERN : Hackathon 2015



THE Port - Hackathon at CERN

"We combine creative minds from CERN and non-profit organisations in interdisciplinary teams to work on humanitarian technology related benefits to society."

Project plan : from prototype to distribution

15

September 2012

From a craft version...

February 2014

Guaranty

June 2014

Pre Production

Certification

..to a 1st industrial version

Next step

- In 2015/2016 :
  - Test in UK and USA
  - Sale in Nepal
- Since may 2017 : sale all over the world
- UK and French common project…starting on December 1st 2017

Thank you for your attention

Questions ?

Calendrier du projet:

- August 2010: Realization of the specifications at the CNOSF (Paris)
- October 2010: Launch of the project implementation at CRITT (Châtellerault)
- October 2010 ~~April~~ 2011: Creation of prototypes for UV protection
- 21 and 22 April 2011: Presentation and testing of prototypes at La Rochelle
- September 2011 ~~April~~ 2012: Realization of the prototype V1
- 7,8 and 9 April 2012: Discount for test of protections (V1) to 15 children of the moon in Poitiers
- 15 April 2012: Test Participation in the Paris marathon with UV protection
- April 2012 September 2012: Tests of protections by the 15 children
- September 2012 March 2014: Improvement of protection and certification to C.E. standards (Châtellerault)
- April 2014 June 2014: Manufacture and assembly of protections (Chauvigny)
- June 2014: Protection of all children in France (100 children
- 5 February 2015: Official delivery of UV protection

XP-FREU(N)DE

The German Speaking Support Group
www.xerodermapigmentosum.de

Alexandra & Christian Moser

General Activities

- Package for new patients
- Information Flyer : Download Link
- How to attach UV protection film to the windows
- Sending material to members & the rest of the world
- Regular alignment confcalls
- Annual meeting with XP patients & their family
- Attending European meetings (ERN, Eurordis)

Agenda

- Who are we and how we operate
- Ideas, Tips & Tricks
- International Activities
- Challenges

Tips & Tricks

- Fundraising activity: xmas card 2017

- Book for kids 4-8 years

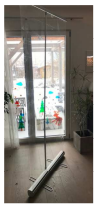
The Group & the team

- 4 familes share organization:
  - finance & admin
  - material & shipment
  - communication: first contact & inquiries, Website, networking, annual group meeting
- 30 families / persons from Germany, Austria, Switzerland, Netherlands

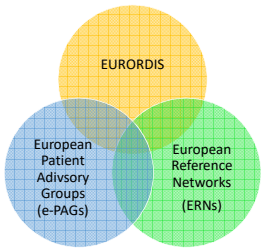
Tips & Tricks cont.

- Skiing helmet ruroc.com

- Rollup with UV protection film



International patient activities in Europe

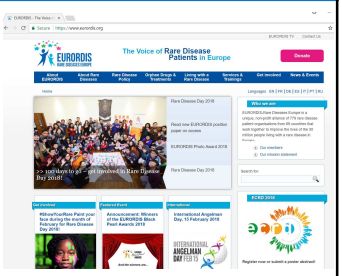


Rareconnect cont.

- Rareconnect.org
- We could setup a free forum for XP patients
- ww coverage possible – however need at least 2-3 European groups to get this started

Eurordis - www.eurordis.org

- Non-Profit Org, supported by the European Union Health Programme (…); but going beyond EU
- Umbrella Organization for over 700 European Self Support Groups
  - We've formally joined now
- 30 employees
- Driving e.g. European Conference on Rare Diseases, Rare Disease Day, Trainings,…
- Providing resources for SSGs



European Reference Networks

Established in March 2017, by the European Commission Health Directorate
- Mainly driven by EU countries

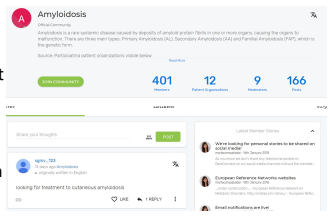
24 ERNs – covering 6000-8000 rare diseases; 300 Hospitals
- ERN Skin
  - 14 Subgroup XP part of DNA Repair subgroup in ERNSkin

Allows Health Care Professionals to work in virtual advisory panels to provide best possible treatments to patients of rare diseases
- access to best specialists

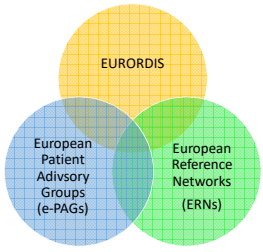
3 IT Platforms
- Public Website
- Patient Exchange
- Clinical patient data exchange across boarders, compliant and private (HCPs only)

Rareconnect

- Rareconnect.org
- Free internet forum for registered patients and patient groups
- Allows to exchange on questions, tips, issues
- Provides automatic translation of posts if required



International patient activities in Europe



E-PAG SKIN: TALENTS & EXPECTATIONS

Matt Bolz-Johnson
Healthcare & Research Director, EURORDIS

Rare Skin ERN Meeting, Paris, 20 November 2017

EURORDIS.ORG

Potential ways and reasons to participate

XP-FREU(N)DE-MONDSCHEINKINDER

Create XP community on Rareconnect	• Need names from 2 other groups in Europe to get started • Once setup, anyone may join
Join Eurordis	• Sign-up on webpage; some €25 annual member fee • For any patient group in Europe • Training, Public relation support
Join the ERNSkin ePAG	• Application letter, Christian may help • ePAG members will elect participants into different Executive Boards for ERNs to make decisions on funding for (research) projects • XP representation in these Exec Boards possible if we get more XP groups to participate

Patients as a 'Patient Resource' invest in ERN

Patient, clinicians and researchers collaboration will be the deciding factor of the success of ERNs.

Four fundamental functions of patient representatives:

- **Unique knowledge or personal experience of a specific disease**
- Only stakeholders **who hold a holistic view of the whole process; only patients have a stake in every stage of the research and healthcare pathways**.
- **Only ones who can to ask anything, as they have often the most relevant and Insightful questions** that should be asked and are often not.
- **Skilled and experienced from other sectors, outside the medical/research field**

EURORDIS.ORG

Closing – Our Challenges

XP-FREU(N)DE-MONDSCHEINKINDER

- Staying in contact with XP teenagers & young adults
- Group participation throughout the year
- No clear standards in terms of support from social security
- Limited funds & time vs. inquires from all over the world
- How to work with media inquiries

- Would love to have support in European networking

European Patient Advocacy Group : Rare Skin ERN

Working Group	ePAG Representative
Epidermolysis Bullosa	• Mikael JAEGA • Ingrid JAGENEAU • Evanina MORCILLO-MAKOW • Clare Robinson • Cinzia Pilo
Ichthyosis & Palmoplantar Keratoderma	• Flavio MINELLI
Ectodermal Dysplasia, Incontinentia Pigmenti & unclassified disorders	• Olivia GROSS-KHALIFA • Ulrike HOLZER • Jacques MONNET • J. M. MONTOYA GUTIERREZ
Monogenic Connective Tissue Disorders	• Marie-Claude BOITEUX • Ivonne RONCHETTI
Cutaneous Mosaic Disorders, Nevi & Nevoid Skin Disorders & Complex Vascular Malformations and Vascular Tumors	• Jodi WHITEHOUSE • Françoise SERIS
Cutaneous diseases related to DNA Repair Disorders	• Ansgar & Michaela JUX • Christian & Alexandra MOSER • Wafa CHAABI
Autoimmune bullous diseases and severe cutaneous drug reactions:	• Sophie LE PALLEC • I. GENTILE
Hidradenitis suppurativa & related syndromes – Behçet – Depso	• Hans-Jörg KUNTE • Bente VILLUMSEN

10/05/2018

EURORDIS.ORG

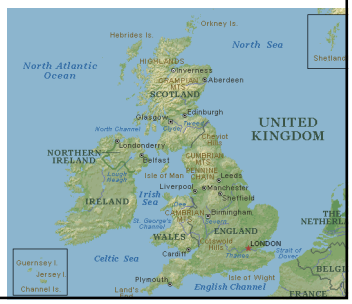
XP-FREU(N)DE-MONDSCHEINKINDER

Thank you!

info@xerodermapigmentosum.de
www.xerodermapigmentosum.de

Setting up a multidisciplinary national XP clinic: the British experience

Dr. Bob Sarkany
and
Dr. Hiva Fassihi



XP in the United Kingdom

- 105 XP patients
- *UK population:* 60 million
- *Prevalence:* 1.8/million

History of the UK Service

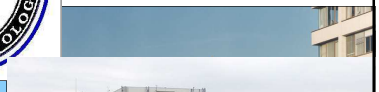
1970s onwards:
Alan Lehmann:
•Research into DNA repair disorders
•Set up DNA repair assay for clinical use

MRC Genome Damage and Stability Centre

1999: Sandra Webb founded XP Support Group

Great Missenden

2006



History of the UK Service

From 1970s: Diagnostic Labs:
Alan Lehmann:
•Research into DNA repair disorders
•Set up DNA repair assay for clinical use

From 1999: Patient Support Group ***(Sandra Webb)***

From 2006: Occasional half day Multidisciplinary Clinic ***(Dermatology, Eyes, Neurology)***

Applying for Government funding for a National XP Service.

A few things helped us …..

- **UK National Health Service (NHS) is nationwide, centrally organised and Government-funded**
- **The NHS supports National Services for very specialised, rare and complicated medical problems**
- **We already had:**
  - **An involved Patient Group**
  - **Diagnostic Laboratories**
  - **A Dermatology Clinic already interested in XP**
- **We applied just before the financial crisis hit Government spending**

We had to prove:

- There was a major need for a National Service

- Our Service would
  - meet this need
  - save money

1) Showing the need for the Service

Submission of the details of the medical care of individual patients were submitted

2) We had to prove that we would

- ***improve key clinical outcomes :***
  1. improved photoprotection to prevent skin cancers.
  2. earlier detection of skin cancers to avoid advanced cancers
  3. improved eye UV protection, early detection of eye disease to avoid visual loss
  4. early detection of hearing loss to enable earlier fitting of hearing aids
  5. detection of early cognitive impairment to enable adjustment of schooling.

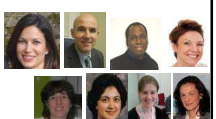
•***'geographical equity':*** provide an equally good service to all patients regardless of where they live in the UK
•***patients' needs and wishes taken into account***
•***an overall cost saving*** for the National Health Service

2010 onwards: NHS 'NCG' funding to establish a National XP Service

Diagnostic Labs:
•DNA Repair (+/- other analyses)
•Next generation sequencing of all 14 DNA repair genes on all patients

Multidisciplinary Clinic

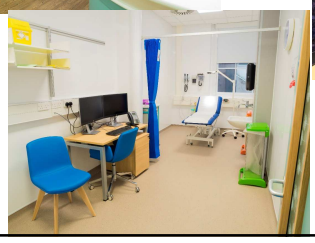
(Photodermatology
Dermatological Surgery
Ophthalmology
Neurology
Neuropsychology
Clinical Genetics
Dermatopathology)



Patient Support Group

Nurse-run outreach network: visiting patients in their homes

2017: a purpose built clinic



HIVA

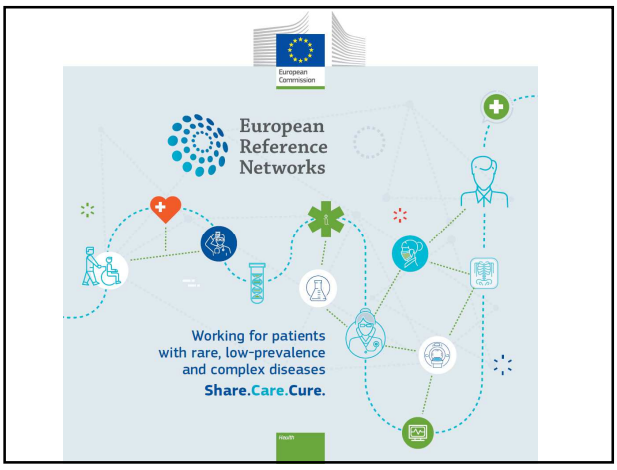
International collaborations in XP.

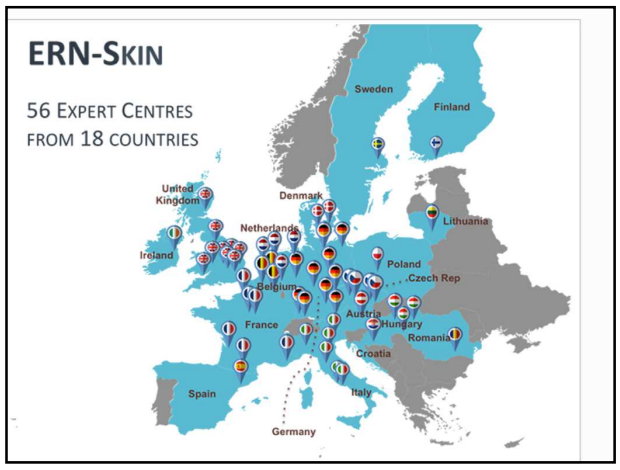
Dr. Bob Sarkany
and
Dr. Hiva Fassihi

HIVA

INTERNATIONAL COLLABORATION:

CLINICAL





European Reference Network
for rare or low prevalence complex diseases
Network Skin Disorders (ERN-Skin)

ERN-Skin

Sub-thematic groups

- Autoimmune bullous diseases and severe cutaneous drug reactions
- Epidermolysis Bullosa
- Ichthyosis & Palmoplantar Keratoderma
- Ectodermal Dysplasia – Incontinentia Pigmenti - Unclassified genetic skin disorders
- Monogenic Connective Tissue Disorders
- Cutaneous Mosaic Disorders - Nevi & Nevoid Skin Disorders and Complex Vascular Malformations and Vascular Tumours
- Cutaneous diseases related to DNA Repair Disorders
- Hidradenitis suppurativa & related syndromes – Behçet – Degos

INTERNATIONAL COLLABORATION:

RESEARCH

Example:

Psychological Study to help to improve UV protection in XP

INTERNATIONAL STUDY RESEARCH TEAM: EUROPE

INTERNATIONAL STUDY RESEARCH TEAM: OUTSIDE EUROPE

INTERNATIONAL COLLABORATION:

HELPING EACH OTHER

Guy's and St Thomas' NHS
NHS Foundation Trust

XP Nursing

Sally Turner (XP Clinical Nurse Specialist Children)
Tanya Henshaw (XP Clinical Nurse Specialist Adults)

Who we are

Sally

Tanya

Guy's and St Thomas' Hospital

Florence Nightingale opened the Nightingale Training School for nurses on 24th June 1860 – aiming to make nursing a respectable profession for women.

General Role of the XP CNS

- Key worker for patients and families
- Advocate, Social services
- Photoprotection advice
- New patients
- Organise all-day multi-disciplinary XP clinics
- Ensure equitable access to service
- Outreach visits to homes, schools, work place and universities

Clinical Nurse Specialist (CNS)

' a clinical nurse specialist is a registered nursing professional who has acquired additional knowledge, skills and experience together with a professionally and/or academically accredited post-registration qualification (if available) in a clinical speciality. They practice at an advanced level and may have sole responsibility for care episode or defined client/group.'

www.rcn.org.uk

General Role of the XP CNS

- Promote awareness of XP at conferences
- Develop patient pathways
- Patient information leaflets
- Research
- Service evaluation and development
- Audit
- Minor skin surgery and diagnostic biopsies
- Camouflage make up

Differences in adult and children's role

Paediatric
- photo protection in schools
- liaising with schools
- liaise with local children's services

Adult
- social services
- education, encouraging adults to protect
- helping in the work place
- multiple surgeries

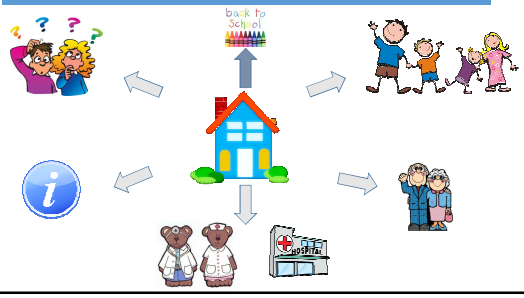
- age appropriate education
- genetic counselling
- neurological degeneration support
- transition
- photoprotection

Work with XP Support Group and Teddington Trust

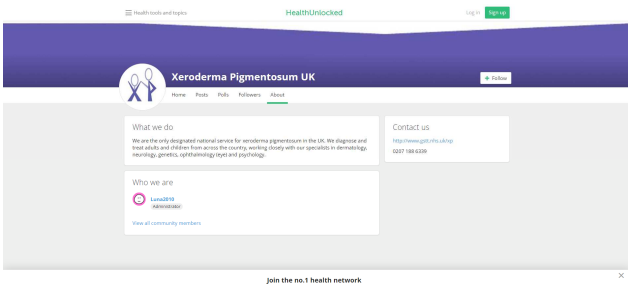
- Day at Owl Patrol each year.
- Contribute to the newsletter
- Collaborate to produce leaflets/educational material
- Meet international families
- Direct patients to support groups as needed

www.guysandstthomas.nhs.uk/xp

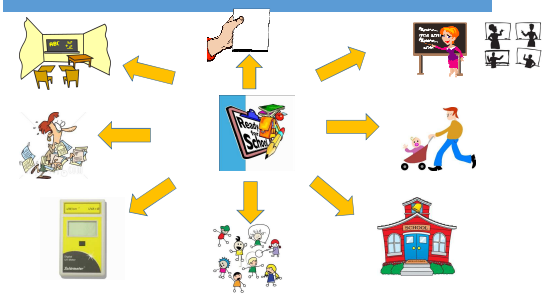
Patient diagnosed with XP
Home visit offered - outreach



https://healthunlocked.com/xp-uk



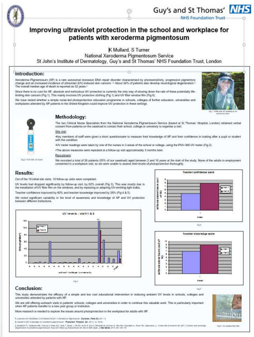
School visits



School visit audit

UVR protection improves in schools and colleges following visits from a XP CNS

- reduced UV levels in key areas by 62%
- increased knowledge 28% and confidence 60% of staff


Guy's and St Thomas' NHS Foundation Trust

Improving ultraviolet protection in the school and workplace for patients with xeroderma pigmentosum

K Mullard, S Turner

National Xeroderma Pigmentosum Service

St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London

Patient Feedback

There is no specialist support locally, so we have nobody else to ask questions about XP.

The combined knowledge in the specialist clinic is incredibly reassuring and helps allay many worries

Meet people with XP, more aware of new products regarding XP I felt everyone knew what they were talking about

The XP Clinic offers the best medical care I have ever received

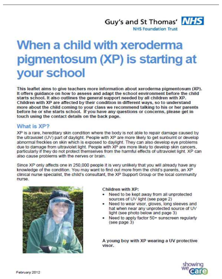
It's an "all in one" clinic so much better than going to several different consultations

Help control XP and understand the problem

Thorough examination by experienced consultants; Aid research in the field; preventative advice and treatment

Teachers study days

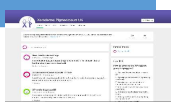
- Written information about XP and Schooling
- XP study days for teachers

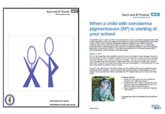

Guy's and St Thomas' NHS Foundation Trust

When a child with xeroderma pigmentosum (XP) is starting at your school

Lessons learnt

- Listen to patients they often have great ideas to improve practice
- Develop information in a variety of forms as it helps to support practice
- Be mindful of differing needs of adults/children/young adults/different cultures when planning care

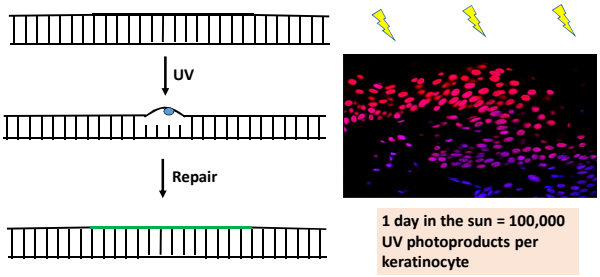




Laboratory testing for XP; research in XP

Alan Lehmann
Genome Damage and Stability Centre
University of Sussex

UV Light damages DNA

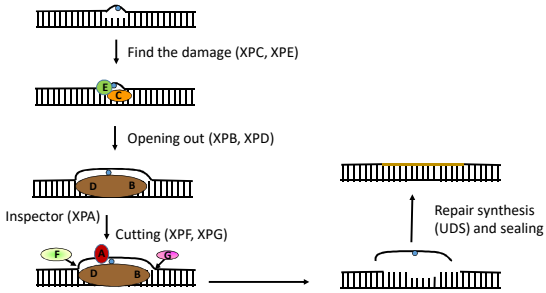


1 day in the sun = 100,000 UV photoproducts per keratinocyte

The genome

- Collection of 25 000 genes containing genetic information
- Stored in DNA molecules
- 23 pairs of chromosomes
- 3 billion building blocks (nucleotide bases)
- Each gene is made up of about 50 000 bases

Mechanism of NER: repairing the track



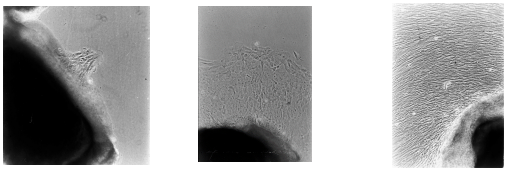
The Problem: Genome Damage

- DNA molecules are very long and fragile
- Damaged in cells at body temperature
- Much more damage on exposure to sunlight, radiation, carcinogens, eg in food
- Leads to loss of genetic information

Measuring NER - XP diagnosis

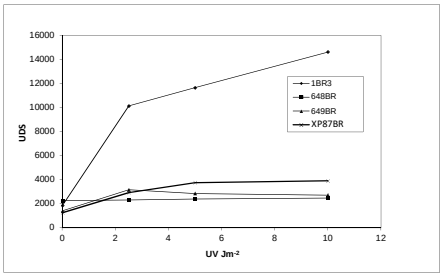
Establishing a cell culture

- Take small skin biopsy
- Cut into pieces – put into flask with growth medium
- Incubate at 37 deg.
- Cells grow out from biopsy into a fibroblast culture, which sticks to plastic surface



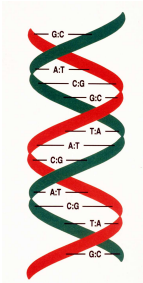
Diagnosis of XP by UDS

- Put cells into dishes
- UV-irradiate
- Incubate (with UDS reagents) to allow repair to take place
- Measure UDS



Tracking down the exact gene mistake in XP

- Eight XP groups (XP-A to G and variant) result from mistakes in one of eight XP genes
- Genes are pieces of DNA made from sequences of just four building blocks (A C G T)



XP variants

- One type of XP has normal UDS – NER is normal - XP variants
- Even in unaffected people NER is quite slow
- Skin cells need to divide before they have repaired all their damage
- Before they divide they have to make a copy of all their DNA
- XP variants have problems copying DNA damaged by UV light and get blocked

Tracking down the exact gene mistake in XP

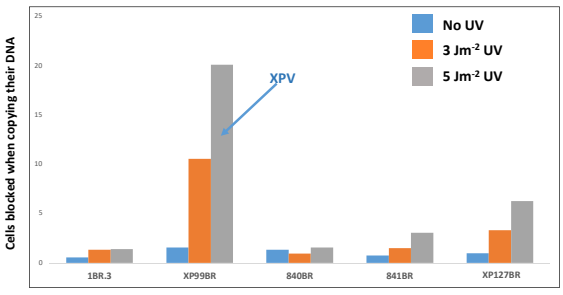
In XP there's a mistake in one of these sequences

Unaffected ACGCGTAGCTATTCCGATGCTA

XP ACGCGTAGCTATTCTGATGCTA

- How do we find the mistake?
- Analyse the sequence of all 8 XP genes
- Find out which one has a mistake and what it is

XP variant test



Tracking down the exact gene mistake in XP

Unaffected ACGCGTAGCTATTCCGATGCTA

XP ACGCGTAGCTATTCTGATGCTA

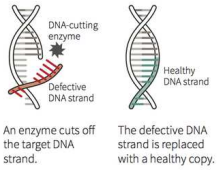
- Enables prenatal diagnosis in affected families
- Enables carriers to be identified in families
- Enables personalised care and management in many cases

Gene therapy: the holy grail

Two Approaches

1. Gene editing – replace the bad gene with a good copy

This can be done in cells in culture.
Not yet in people

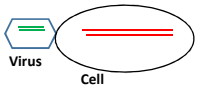


An enzyme cuts off the target DNA strand.

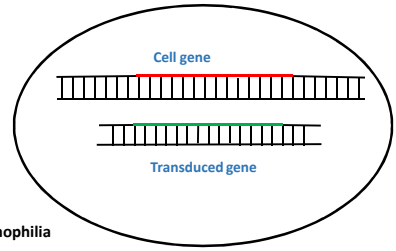
The defective DNA strand is replaced with a healthy copy.

Gene therapy: the holy grail

2. Gene transduction: wrap the good gene in a virus coat and put into cells.



Good gene sits in cells with bad gene and is able to make good protein



This works in cells

And in people with haemophilia

Gene therapy: will it work for XP?

? Delivery of corrected cells to skin and to brain

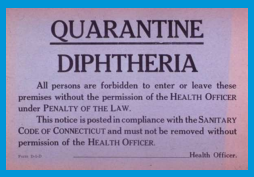
National Cancer Institute

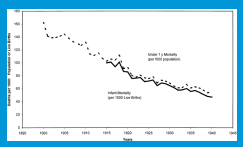
DNA Repair Research at the National Institutes of Health

Deborah Tamura MS, RN, APNG
NIH, NCI, CCR, LCBG
National Cancer Institute
Bethesda, MD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

A Little US History …. And How the NIH Came to be





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No conflicts of interest.

United States – A Country of Immigrants

National Cancer Institute

United States of America

National Cancer Institute

Health Problems In 1885-1900

- ta
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- ng
- f Influenza,
- nd Cholera

Overcrowding and disease – ¼ of babies in NYC's immigrant neighborhoods died by age 1.

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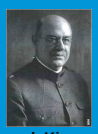
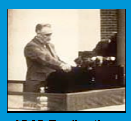
Brief History of NIH

- 1887 Laboratory of Hygiene established at Marine Hospital, Staten Island NY – prevent import of epidemics
- 1930 Hygienic laboratory renamed National Institute of Health – first system of fellowships established.
- 1937 The National Cancer Institute established
- 1940 NIH Campus in 'rural Maryland'



Joseph Kinyoun M.D.



1940 Dedication of NIH Campus

National Cancer Institute

Overview of the NIH

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XP patients see health care professionals from:

- NCI – National Cancer Institute
- NEI – National Eye Institute
- NHGRI – National Human Genome Research Institute
- NINDS – National Institute of Neurologic Disorders and Stroke
- NIDCD – National Institute of Deafness and Communication Disorders
- NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases
- NCMRR - National Center for Medical Rehabilitation Research

ties

National Cancer Institute

Brief History of NIH

- 1946 NIH established process of grants and fellowships to non-federal institutions
- 1948 National Heart Institute, National Microbiological Institute, Experimental Biology and Medicine Institute and National Institute of Dental Research established – renamed National Institutes of Health
- 1953 Clinical Center (Building 10) opened

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Research Studies Funded by the NIH

- **Patient-oriented research:** involves a particular person or group of people or uses materials from humans.
- **Epidemiological and behavioral studies**
- **Outcomes and health services research**

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Xeroderma Pigmentosum Research at the NIH

1953 – Watson and Crick describe double helix DNA structure
1964 – Setlow and Hanawalt separately describe DNA repair replication in bacteria
1968 – James Cleaver describes DNA repair defect in XP

NATURE, VOL. 218, MAY 18, 1968

Defective Repair Replication of DNA in Xeroderma Pigmentosum

by

J. E. CLEAVER

Laboratory of Radiobiology, University of California Medical Center, San Francisco, California

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.

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Xeroderma Pigmentosum

Understanding Xeroderma Pigmentosum

Review Article (*Arch Dermatol* 1987;123:241-250)

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. Cuta-

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,

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Xeroderma Pigmentosum Research at the NIH

1974

NIH Conference

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. COOK, Ph.D. Bethesda, Maryland

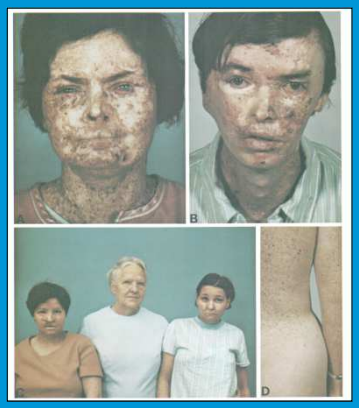
February 1974 • Annals of Internal Medicine • Volume 80 • Number 2

Long Time Partners

Dr. John J. DiGiovanna

National Cancer Institute

First XP Patients Studied at NIH



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Skin Cancer Chemoprevention

- Oral retinoids to prevent skin cancer in XP patients

The Journal of Dermatology
Vol. 19: 715–718, 1992

WS II-7

Chemoprevention of Skin Cancer in Xeroderma Pigmentosum

Kenneth H. Kraemer, John J. DiGiovanna* and Gary L. Peck*

was stopped.

- However, there were many side effects

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Xeroderma Pigmentosum Research at the NIH - Workshops

- Representatives and patients from DNA repair disorder support groups attended meetings.
- First time many bench scientists had met patients with the conditions they studied.
- Patients and their families discussed what research they would like pursued.
- Research as a collaborative effort between scientists and patients.

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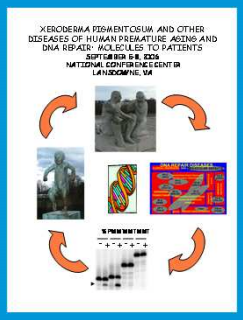
Xeroderma Pigmentosum Research at the NIH – DNA Repair Workshop - 2006



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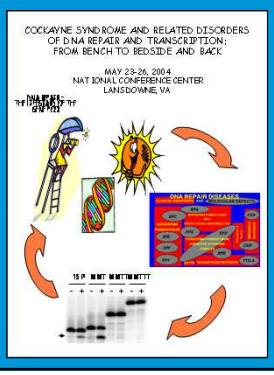
Xeroderma Pigmentosum Research at the NIH – DNA Repair Workshop 2004



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Xeroderma Pigmentosum Research at the NIH

Attendees at 2006 Meeting

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Xeroderma Pigmentosum Research at the NIH – DNA Disease Repair Workshop - 2004

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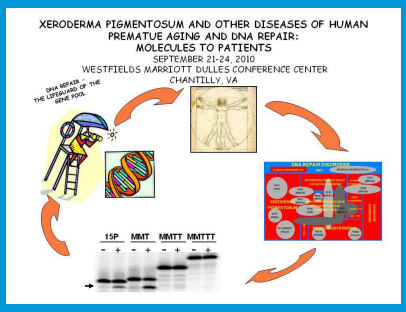
Xeroderma Pigmentosum Research at the NIH – DNA Repair Workshop 2010



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Xeroderma Pigmentosum Research at the NIH

Attendees at 2010 Meeting

National Cancer Institute

Current DNA Repair Studies: XP, TTD and CS

MEDICAL RECORD | CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: National Cancer Institute

STUDY NUMBER: 99-C-0099 PRINCIPAL INVESTIGATOR: Kenneth H. Kraemer, M.D.

STUDY TITLE: Examination of Clinical and Laboratory Abnormalities in Patients with Defective DNA Repair: Xeroderma Pigmentosum, Cockayne Syndrome, or Trichothiodystrophy

Continuing Review Approved by IRB on 05/21/12
Amendment Approved by IRB on 07/28/11 (H) Date Posted to Web: 06/06/12
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:
Taking part in NIH research is entirely voluntary.

Study of people with XP, TTD and Cockayne syndrome

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Xeroderma Pigmentosum Research at the NIH

National Cancer Institute

Current DNA Repair Studies: XP, TTD and CS

MEDICAL RECORD | CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: National Cancer Institute

STUDY NUMBER: 02-C-0313 PRINCIPAL INVESTIGATOR: Kenneth H. Kraemer, M.D.

STUDY TITLE: Cancer Risk in Xeroderma Pigmentosum Heterozygotes

Continuing Review Approved by the IRB on 01/23/12
Amendment Approved by the IRB on 12/5/09 (D) Date Posted to Web: 02/02/12
XP Adult

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:
Taking part in NIH research is entirely voluntary.

Study of XP family members

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Xeroderma Pigmentosum Research at the NIH

- More than 200 XP research papers have been published by scientists at the NIH
  - Clinical research
  - Laboratory research
  - Review articles for clinical care
- About 50 research papers on other conditions of DNA repair have also been published
- Research Collaboration with the NEI, NHGRI, NIDCD, NIAID, NIA, NIMH, NINDS, NICHD, NHLBI
- Collaborations with scientists through out the world
- Monthly DNA Repair Interest Group videoconferences videocast.nih.gov
- Almost 5,000 articles listed in PubMed relating to xeroderma pigmentosum

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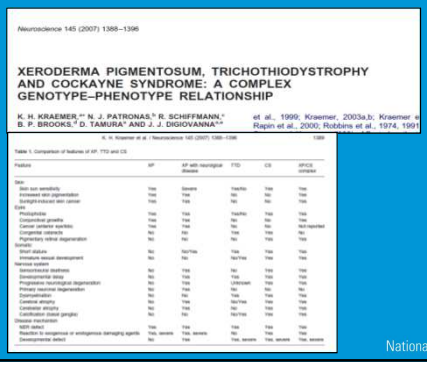
Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?



Neuroscience 145 (2007) 1388–1396

XERODERMA PIGMENTOSUM, TRICHOTHIODYSTROPHY AND COCKAYNE SYNDROME: A COMPLEX GENOTYPE–PHENOTYPE RELATIONSHIP

K. H. KRAEMER,[a]* N. J. PATRONAS,[b] R. SCHIFFMANN,[c] B. P. BROOKS,[d] D. TAMURA[e] AND J. J. DIGIOVANNA[e,f]

et al., 1999; Kraemer, 2003a,b; Kraemer
Rapin et al., 2000; Robbins et al., 1974, 199

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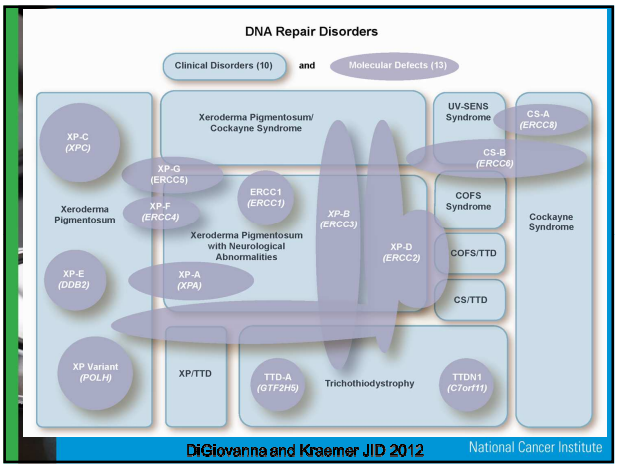
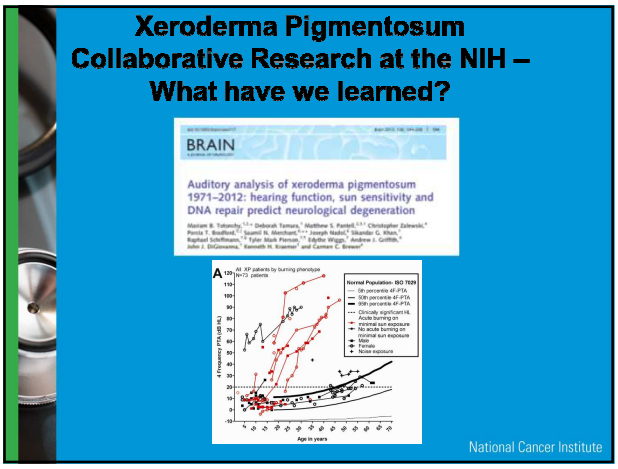
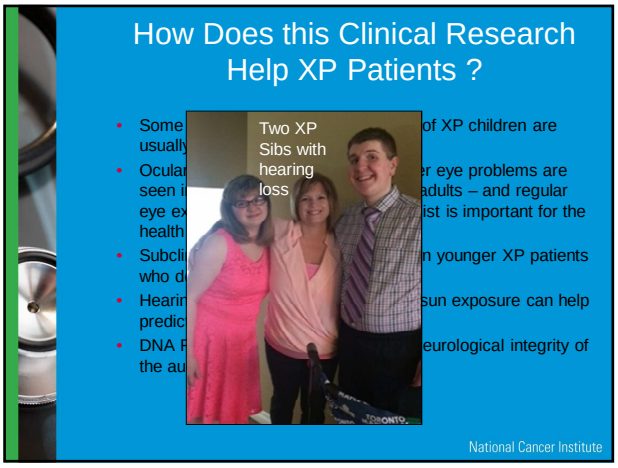

DNA Repair Disorders
Clinical Disorders (10)
and
Molecular Defects (13)
XP-C (XPC)
Xeroderma Pigmentosum/ Cockayne Syndrome
UV-SENS Syndrome
CS-A (ERCC8)
CS-B (ERCC6)
XP-G (ERCC5)
ERCC1 (ERCC1)
XP-F (ERCC4)
XP-B (ERCC3)
Xeroderma Pigmentosum
Xeroderma Pigmentosum with Neurological Abnormalities
XP-D (ERCC2)
COFS Syndrome
Cockayne Syndrome
COFS/TTD
XP-E (DDB2)
XP-A (XPA)
CS/TTD
XP Variant (POLH)
XP/TTD
TTD-A (GTF2H5)
Trichothiodystrophy
TTDN1 (C7orf11)
DiGiovanna and Kraemer JID 2012
National Cancer Institute


Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?
BRAIN
Auditory analysis of xeroderma pigmentosum 1971–2012: hearing function, sun sensitivity and DNA repair predict neurological degeneration
National Cancer Institute


How Does this Clinical Research Help XP Patients ?
Some
of XP children are
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Ocular
r eye problems are
seen i
adults – and regular
eye ex
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health
Subcli
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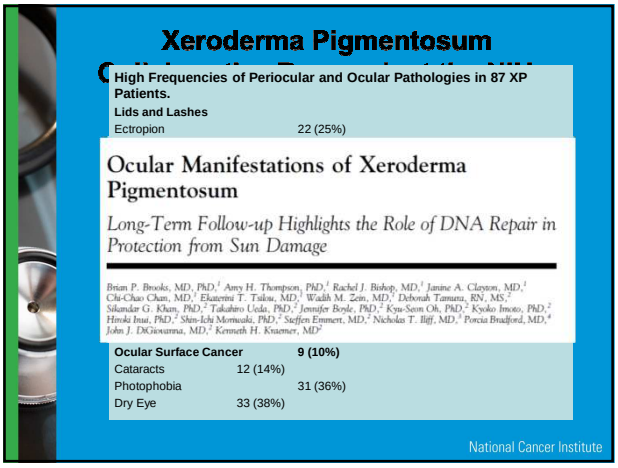
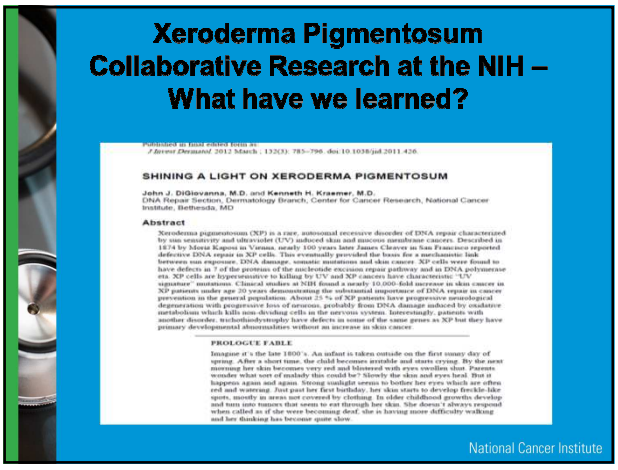
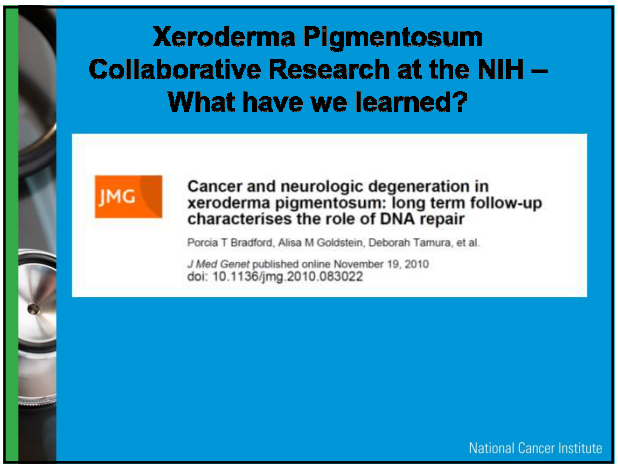
who d
Hearin
sun exposure can help
predic
DNA R
eurological integrity of
the au
Two XP Sibs with hearing loss
National Cancer Institute


Xeroderma Pigmentosum
High Frequencies of Periocular and Ocular Pathologies in 87 XP Patients.
Lids and Lashes
Ectropion 22 (25%)
Ocular Manifestations of Xeroderma Pigmentosum
Long-Term Follow-up Highlights the Role of DNA Repair in Protection from Sun Damage
Ocular Surface Cancer 9 (10%)
Cataracts 12 (14%)
Photophobia 31 (36%)
Dry Eye 33 (38%)
National Cancer Institute


Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?
SHINING A LIGHT ON XERODERMA PIGMENTOSUM
John J. DiGiovanna, M.D. and Kenneth H. Kraemer, M.D.
Abstract
PROLOGUE FABLE
National Cancer Institute


Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?
JMG
Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair
Porcia T Bradford, Alisa M Goldstein, Deborah Tamura, et al.
J Med Genet published online November 19, 2010
doi: 10.1136/jmg.2010.083022
National Cancer Institute

Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?

ARTICLE

GTF2E2 Mutations Destabilize the General Transcription Factor Complex TFIIE in Individuals with DNA Repair-Proficient Trichothiodystrophy

Christiane Kuschal,[1,6,10] Elena Botta,[2,8] Donata Orioli,[2,8] John J. Digiovanna,[1] Sara Seneca,[3] Kathelijn Keymolen,[3] Deborah Tamura,[1] Elizabeth Heller,[1] Sikandar G. Khan,[1] Giuseppina Caligiuri,[2] Manuela Lanzafame,[2] Tiziana Nardo,[2] Roberta Ricotti,[2] Fiorenzo A. Peverali,[2] Robert Stephens,[4,5] Yongmei Zhao,[5] Alan R. Lehmann,[6] Laura Baranello,[7] David Levens,[7] Kenneth H. Kraemer,[1,9,*] and Miria Stefanini[2,9,*]

The general transcription factor IIE (TFIIE) is essential for transcription initiation by RNA polymerase II (RNA pol II) via direct interaction with the basal transcription/DNA repair factor IIH (TFIIH). TFIIH harbors mutations in two rare genetic disorders, the cancer-prone xeroderma pigmentosum (XP) and the cancer-free, multisystem developmental disorder trichothiodystrophy (TTD). The phenotypic complexity resulting from mutations affecting TFIIH has been attributed to the nucleotide excision repair (NER) defect as well as to impaired transcription. Here, we report two unrelated children showing clinical features typical of TTD who harbor different homozygous missense mutations in *GTF2E2* (c.448G>C [p.Ala150Pro] and c.559G>T [p.Asp187Tyr]) encoding the beta subunit of transcription factor IIE (TFIIEβ). Repair of ultraviolet-induced DNA damage was normal in the *GTF2E2* mutated cells, indicating that TFIIE was not involved in NER. We found decreased protein levels of the two TFIIE subunits (TFIIEα and TFIIEβ) as well as decreased phosphorylation of TFIIEα in cells from both children. Interestingly, decreased phosphorylation of TFIIEα was also seen in TTD cells with mutations in *ERCC2*, which encodes the XPD subunit of TFIIH, but not in XP cells with *ERCC2* mutations. Our findings support the theory that TTD is caused by transcriptional impairments that are distinct from the NER disorder XP.

New TTD Gene

XP Expert Resource Group

- Annual meeting at the American Academy of Dermatology
- Dermatologists present newly diagnosed or follow-up information on XP patients
- Discuss treatments
- Members of the XP support groups are invited and present patient/family centered information.

Read through of Stop Codons by use of Aminoglycosides in Cells from Xeroderma Pigmentosum Group C Patients. Experimental Dermatology 24: 296-7 Christiane Kuschal et.al. (2015).

- Read through of premature termination (stop) codons (PTC) is a new approach to treatment of genetic diseases. We recently reported that read through of PTC in cells from some xeroderma pigmentosum complementation group C (XP-C) patients could be achieved with the aminoglycosides geneticin or gentamicin.
- Clinical and cellular studies, have been conducted in several human diseases including Duchenne muscular dystrophy and cystic fibrosis, with variable results.
- There was a significant increase in post-UV cell survival following G418 treatment for TGA-A1,2 cells and TAG-A1 cells – **XPC cells with premature stop codons** but not with paromomycin treatment.
- In selected XP patients, topical PTC therapy can be investigated as a method of personalized medicine to alleviate their cutaneous symptoms.

Xeroderma Pigmentosum Collaborative Research at the NIH – Next Steps

- Continue to investigate neurodegenerative disease
- Investigate better treatment methodologies
- Investigate non-dermatological features of XP

Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?

Looking to the Future: XP Research Can't Continue Without you

KRAEMER LAB	MED ICAL STUDENTS	COLLABORATORS		
Sikandar Khan	Christine Liang	NIH- CLINICAL	NIH- LAB	FOREIGN
Christiane Kuschal	Andrea Morris	Tom Hornyak	Paul Meltzer- NCI	Shin-ichi Moriwaki - Japan
Taro Masaki	Tara Rao	Nicholas Patronas	Tom Schneider - NCI	Steffen Emmert – Germany
Kyoko Imoto	Salma Faghri	Suvimol Hill	Vilhelm Bohr - NIA	Hanoch Slor – Israel
Hiroki Inui				Gozukara - Turkey
Takahiro Ueda				Stefanini – Italy
Kyu Seon Oh				Jaspers – erlands
Seiji Takeuchi				Joe|makers – erlands
Yun Wang				Lehmann - UK
Xiaohui (Jane) Tan				Tanaka – Japan
Jennifer Boyle				ko Nishigori - Japan
CLINICAL				Hirai - Japan
John DiGiovanna				Marc Egly - France
Deborah Tamura				Sarasin - France

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Xeroderma Pigmentosum Collaborative Research at the NIH – What have we learned?

XP: Defect in nucleotide excision repair

Complementation Group	Gene	Locus	Percentage
XPA	XPA	9q22.3	29.4%; most common in Japan
XPB	XPB ERCC3	2q21	0.5%
XPC	XPC	3p25	27.3%; most common in US
XPD	XPD ERCC2	19q13.2-q13.3, 10q11	15.0% most common with neurologic disease
XPE	DDB2	11p12-p11	1.1%
XPF	XPF ERCC4	16p13.3-p13.13	1.6%
XPG	RAD2 ERCC5	13q33	1.1%
XPV	POLH	6p21.1-p12	24.1%

Modified from: Kraemer KH et al. Xeroderma Pigmentosum. *Arch Dermatol* 1987; 123: 241-250.

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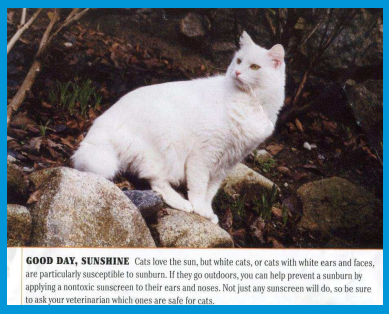
Your Cat Trivia for the Day



GOOD DAY, SUNSHINE Cats love the sun, but white cats, or cats with white ears and faces, are particularly susceptible to sunburn. If they go outdoors, you can help prevent a sunburn by applying a nontoxic sunscreen to their ears and noses. Not just any sunscreen will do, so be sure to ask your veterinarian which ones are safe for cats.

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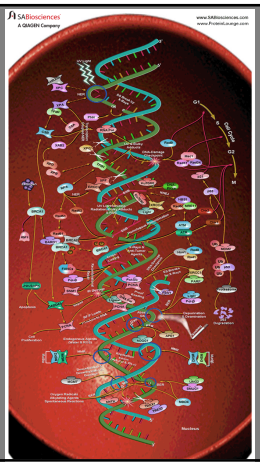
United States in Early 1900's

- 1900 to 1915 – more than 15 million immigrants came to US
- Most came from southern and eastern Europe - Italy, Poland, Russia
- 1910 – ¾ of New York City's population were immigrants or first generation Americans

National Cancer Institute

DNA Repair Pathways



Health Care in Early 1900's

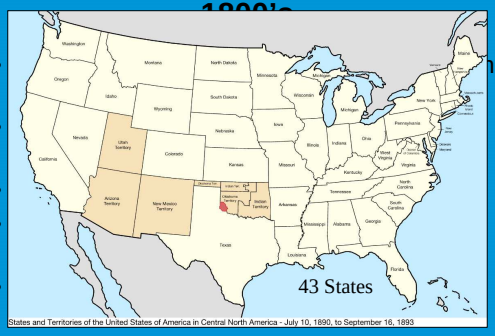
National Cancer Institute

Early Years of the NIH

- **1912 Public Health Service established**
- **1921 Rocky Mountain Spotted Fever Laboratory established in Montana – first of the Public Health Field stations**

National Cancer Institute

The United States in the Late



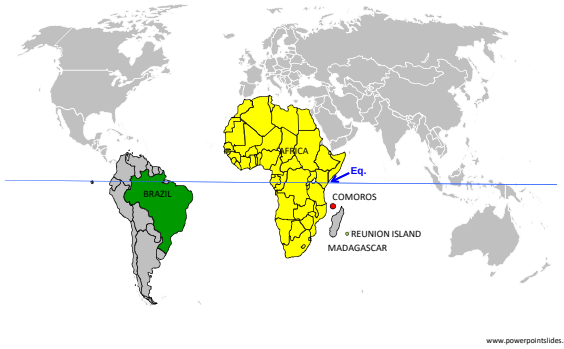
States and Territories of the United States of America in Central North America - July 10, 1890, to September 16, 1893

National Cancer Institute

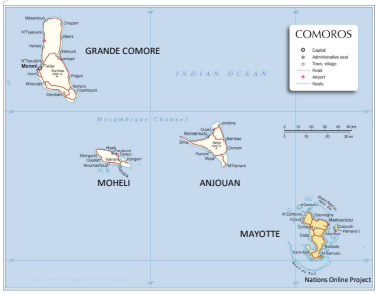
How History and Geography caused the high incidence of Xeroderma Pigmentosum-C patients in the Comorian Archipelago

Alain SARASIN
Gustave Roussy Institute
CNRS, University Paris-Sud
Villejuif, France
alain.sarasin@gustaveroussy.fr

ARCHIPELAGO OF COMOROS



THE ISLAND OF ANJOUAN



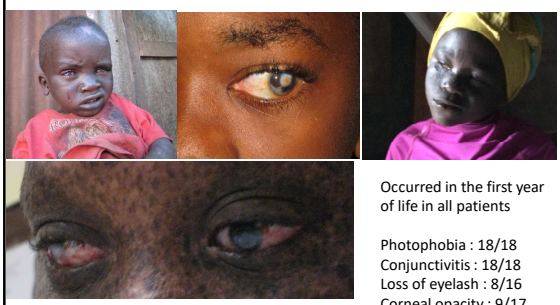
- Very high incidence (around 1/5000) of black-skinned XP patients in the Comorian population, but ONLY in the Anjouan Island.
  Islands: closed environment and remarkable degree of inbreeding
- 1/50,000 in North Africa and the Middle East
- 1/100,000 in Japan
- 1/1,000,000 in the United States and Europe

Islamic Federal Republic of the Comoros: Gross Domestic Product per Capita is $700 (60x less than in Mayotte)

COHORT OF COMORIAN BLACK-SKINNED XP PATIENTS

- Among 32 registered patients, we have followed a group of 18 black-skinned XP patients
- All from one island (Anjouan) in the Comorian Archipelago
- With early ocular and cutaneous features
- None presented dysmorphic features or growth retardations
- Neurological status and psychomotor development were normal

OCULAR FEATURES



Occurred in the first year of life in all patients

Photophobia : 18/18
Conjunctivitis : 18/18
Loss of eyelash : 8/16
Corneal opacity : 9/17
Visual acuity <5/10 : 8/16
Blind : 5/16 before the age of 10

The first symptom was ocular in 83% of patients

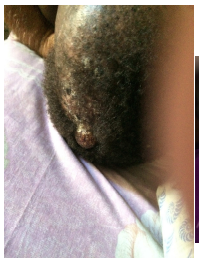
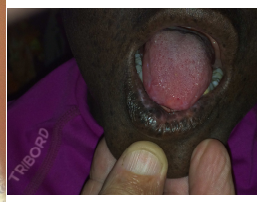
Photographs with authorization

CUTANEOUS FEATURES

- All patients have classical and severe skin abnormalities including xeroses, actinic keratoses, telangiectasies, atrophy and hypo/hyper-pigmentary aspects giving a « salt and pepper pattern » that covered more than 50% of sun-exposed areas
- Erythroplakia on the tip of the tongue (sun-exposed)
- Often severe actinic chelitis of the upper or lower lips

Photographs with authorization

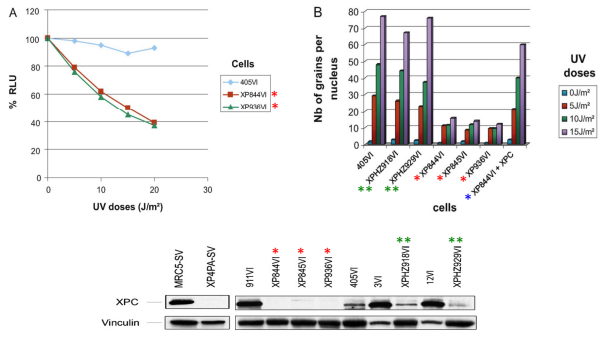
Skin tumours in black-skinned XP-C patients

Essentially SCC and BCC on sun exposed areas: top of the head, nose and tip of the tongue
Very seldom malignant melanoma (black skin)

Photographs with authorization

Characterization of diploid fibroblasts from the Comorian XP patients

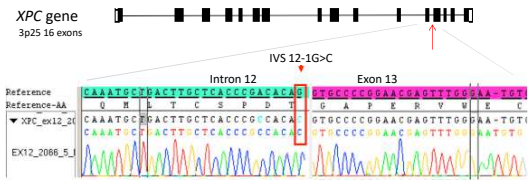


The Comorian XP cells (*) are UV-sensitive, very low Unscheduled DNA Synthesis, no XPC protein by Western analysis and are complemented for UDS following infection by recombinant retroviruses expressing wild-type *XPC* cDNA (*). The heterozygous parents (**) have normal UDS but expressed lower level of XPC protein than controls.

Cartault et al., DNA Repair, 2011, 10, 577-585.

MOLECULAR ANALYSIS

- We found a unique G>C homozygous substitution in the 3' end of the XP intron 12 in all patients (**IVS 12-1G>C, c.2251-1G>C**)
- All parents were heterozygous G/C
- This substitution was not found in a series of 55 healthy controls from Comoros
- This mutation was never described previously (<2011)
- Three *XPC* mRNA isoforms were found, no XPC protein

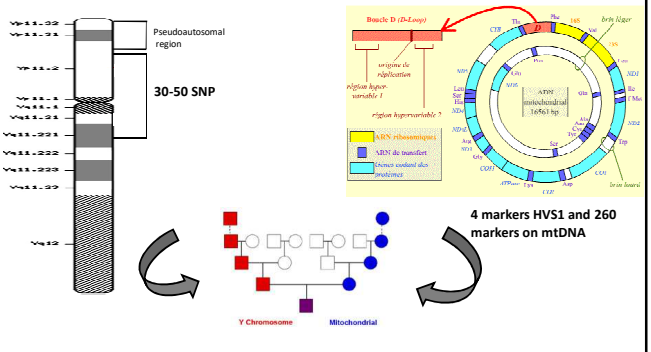


A unique mutation in all patients from the Comoros

Cartault et al., DNA Repair, 2011, 10, 577-85.

2-A specific mutation originated from the African Bantu population

GENETIC AND ETHNIC FOLLOW UP OF THE XP-C PATIENTS: Y CHROMOSOMAL AND MITOCHONDRIAL GENETIC VARIATIONS



4 markers HVS1 and 260 markers on mtDNA

Analysis of mitochondrial DNA markers in the XP-C Comorian population

mtDNA			
DNA	Status	Haplogroup	Origin
3003	Patient	L1c	West-central africa
3538	Patient	L0a2	South-East Africa
7961	Patient	L1c2a1	West-central africa
9199	Patient	L1c2a1	West-central africa
7053	Patient	L3e3	West africa
2068	Patient	L3d1a1a	west-central africa
2067	Patient	L3e3	West africa
3124	Patient	L3e3	West africa
1949	Patient	L2a1	South Africa
7888	Patient	L3f1b4a	East africa Sahel Zone
9826	Patient	L0a2	South-East Africa
2629	Patient	L3b	West Africa
AS970	Patient	L0d1b	Austral Africa

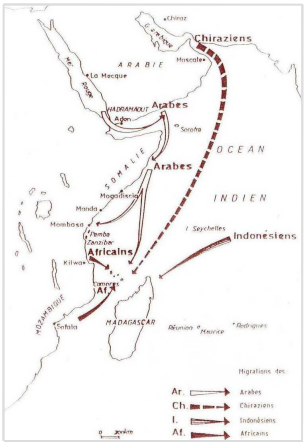
all patients have an African origin by their mother

ANALYSIS OF Y CHROMOSOME IN COMORIAN POPULATION

Y CHROMOSOME					
DNA	Status	Mutations	variations	Haplogroup	Origin
3003	patient	L514	C > T	E1b1a1a1f1	West-central africa
3538	patient	L514	C > T	E1b1a1a1f1	West-central africa
7961	patient	L485	C > T	E1b1a1a1f	West-central africa
9199	patient	L485	C > T	E1b1a1a1f	West-central africa
7053	patient	M191	T > G	E1b1a1a1f1a	West-central africa
2068	patient	Z827	G > C	E1b1b1b	nord-west africa
2067	patient	M92	C > T	J2a1b1	East Africa
3124	patient	M92	C > T	J2a1b1	East Africa
1949	patient	M54	A > G	E2b	South-West-East Africa
7888	patient	P278.2	A > G	R1a1a1b1a2b1	Eurasia
9826	patient	P278.2	A > G	R1a1a1b1a2b1	Eurasia
2629	patient	L485	C > T	E1b1a1a1f	West-central africa
AS970	Patient control	L485	C > T	E1b1a1a1f	West-central africa

The majority of XP-C patients have an African origin by their father

Migration of different ethnic population to Comoros Islands

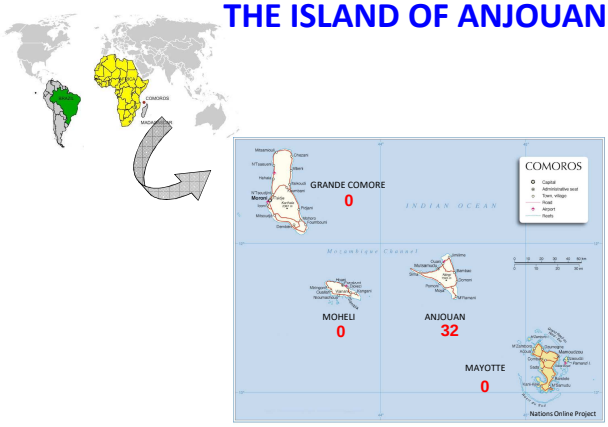


-Arrival of the African Bantu population between 7-10th centuries

-Arrival of the Arabs from the Arabic Peninsula and from Chirazia around 11-13th centuries (700-800y from now)

AS2712

THE ISLAND OF ANJOUAN

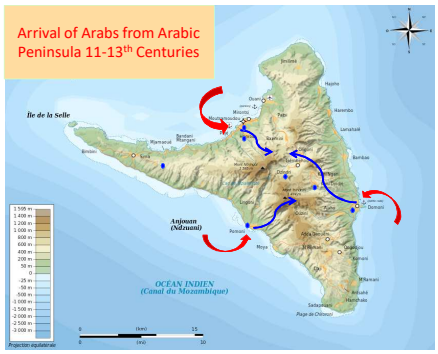


Nb of XP patients ORIGINATED from:

We have recently found this mutation among XP patients from Kenya and it has also been described for South Africa.

Why XP-C patients are only present in the *island of Anjouan* although the 4 islands have been peopled by the same individuals coming from East Africa (Mozambique, Tanzania, Kenya, South Africa) during the 7-10th centuries?

Current localization of XP-C families in Anjouan



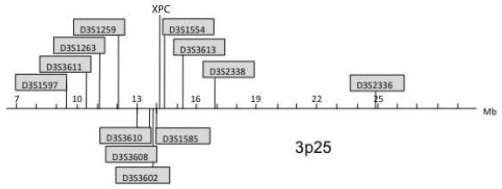
-At the arrival of the Arabs some black individuals in Anjouan refused to be under slavery
-So they fled and hid themselves inside the island of Anjouan protected by volcanic mountains
- if XP heterozygous individual(s) were concerned: Consanguinity, poverty, absence of migration to the other islands= high frequency of XP-C patients and only in Anjouan

AS2715bis Eng

ESTIMATION OF THE AGE OF THE MUTATION IVS 12-1G>C IN COMORIAN POPULATION

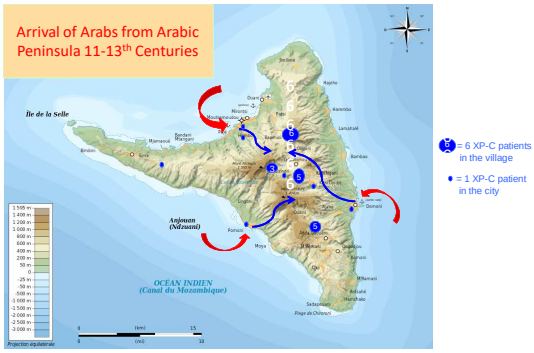
•We used 8 microsatellite markers surrounding the *XPC* gene spanning 21.21 cM
•We genotyped 13 homozygous patients and 6 parents

•Taking into account the frequency of recombination at these sites: the age of the mutation was estimated to be around 770 years B.P. (614-945) assuming a 25-year generation time. This is highly suggestive that some specific event arrived around 800y in these islands.



F.Austerlitz et al, Genetics, 2003, 165, 1579-1586
Cartault et al., DNA Repair, 2011, 10, 577-85

Current localization of XP-C families in Anjouan



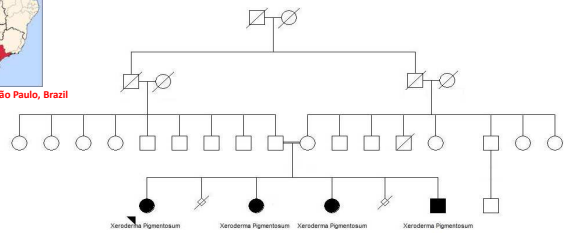
-Even now (2016), the XP-C patients live in the same villages far from the roads and from the sea, probably since 800 years.

AS2715bis Eng.

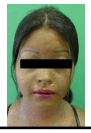
3-A common mutation between Comorian islands and Brazil?

Consanguineous Brazilian family with the *XPC* mutation of Comoros (Coll. Dr. Maria Isabel Achatz, National Cancer Institute, Sao Paulo)

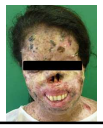
Place of origin: São Paulo, Brazil



Sample: XP10
Birth Date: July 7, 1987
Mutation: c.2251-1G>C homozygous



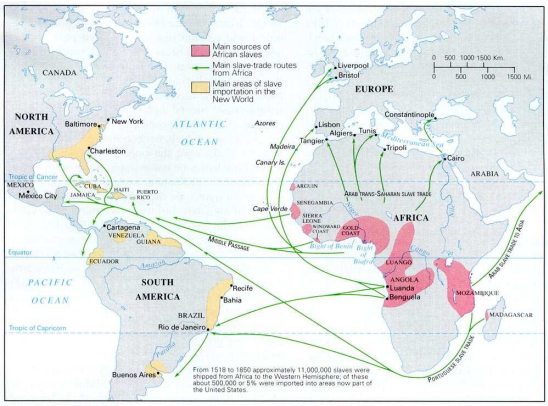
Sample: XP9
Birth Date: June 16, 1981
Mutation: c.2251-1G>C homozygous



African Haplogroups

AS2736 Eng.

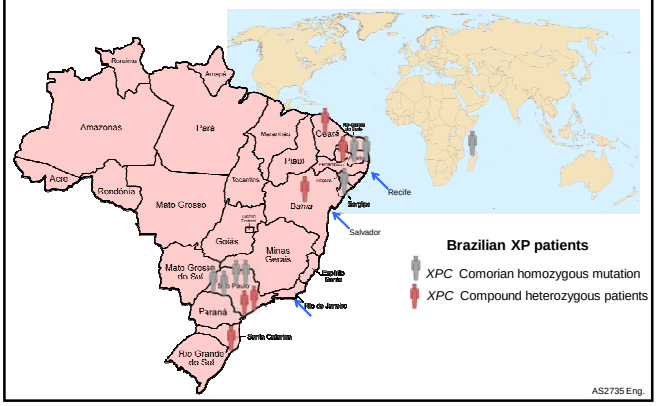
Seaborne slave trades between Africa and South America



During the 18-19th centuries, 20% of black African slaves in Brazil came from East Africa, mainly from the Portuguese colony Mozambique. These slaves were called ("The Moçambicos"). They have the same ethnic origins as the population of Anjouan.

AS2718

Distribution of the *XPC* Comorian mutation in Brazil (Gift of Dr. Maria Isabel ACHATZ)



AS2735 Eng.

Map of the slave trading across the Indian Ocean and the Atlantic Ocean

Museu Naval

Rio de Janeiro

Painting

18th Century

AS2737 Eng.

CONCLUSIONS

*A very high incidence of XP-C patients was found in the Comoros Archipelago, but, in fact, only originated from the Anjouan island. These patients should arrived from Central Africa during the migration of some Bantu individuals toward east. Indeed, XP patients from East Africa have been found with the same mutation.

*These patients are black and their skin is relatively protected from skin cancers (particularly malignant melanoma) taking into account they are living close to the equator and that they did not really protect themselves.

*The first and irreversible symptoms of these patients are on the eyes leading to blindness very rapidly. Black melanin is not active in this organ.

*Historical and geographical reasons seem to explain the presence of XP-C patients only in Anjouan to flee slavery during the Arabic period.

*Although the mutation found in these Comorian patients had never been described before, some XP-C patients with exactly the same mutation and with Central African haplotypes have been found in Brazil. The existence of boats of slaves between Mozambique and Rio de Janeiro may explain this relationship.

THANKS TO

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François CARTAULT
Nadia DJERIDI
Patrick MUNIER
Patrick N'GUYEN

Coll. with the Mayotte Hospital

Joelle PARIAUD
Philippe PARIAUD

Collaboration

Maria Isabel ACHATZ (Sao Paulo, Brazil)
Fréderic AUSTERLITZ (Paris)
Sophie BLANCHY (Paris)
Ned ALPERS (UCLA, USA)

Differences between black- and white-skinned XP-C patients

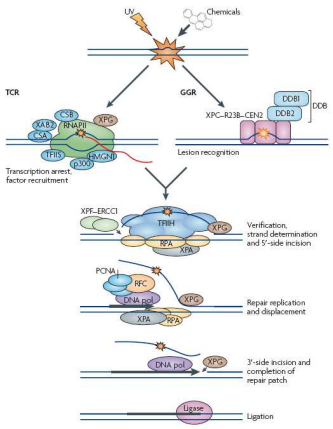
Clinical symptoms	Black-skinned XP-C* (Comoros; Latitude -12°)	Caucasian XP-C** (North Africa; Latitude +30°)
Ocular damage	100% early; 50% blind before 10y.	40% after 10y.
Cutaneous tumours	50%; mean age: 4.5y.	78%; mean age: 4.7y.
Cancers on the tip of the tongue and eyes	Frequent	Uncommon
Malignant melanoma	Rare	Frequent
Life expectancy	< 13y.	>15y.
	* Cartault et al., DNA Repair, 2011, 10, 577-585.	**Hadj-Rabia et al., Br. J. Derm., 2013, 168, 1109- 1113.

* and **: No XPC protein

The black-skinned XP patients develop rarely melanoma confirming the role of melanin in protecting individuals. They developed carcinoma but less than the Caucasians taking into account the latitude. However, they have rapid and irreversible eye problems, which are not protected by melanin.

AS2717

NER: Transcription-Coupled Repair and Global Genomic Repair



Defective TCR:
Increased cell death
Increased aging:
CS, XP/CS, TTD

Defective GGR:
Increased mutations
Increased cancer:
XP, XP/CS

Hanawalt & Spivak,
Nature Rev. Mol. cell Biol., 2008, 9, 958-970

AS2389''

Aim of this study

1- Description of the cohort of XP-C patients from Comorian islands

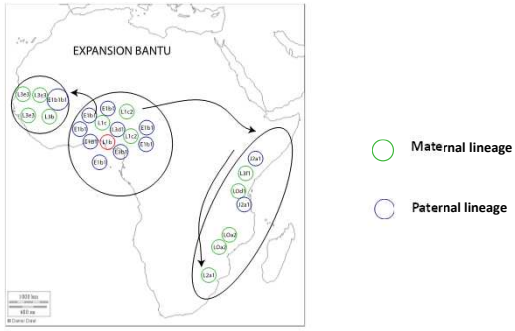
- Clinical description
- UV-sensitivity, UDS, retroviral complementation
- Differences between black- and white-skinned XP patients

2- A specific mutation originated from the African Bantu population

- Analysis of the ethnic origins of the XP patients according to the Y-markers and the mtDNA sequence
- XP-C patients are located only in the island Anjouan

4- A common mutation between Comorian islands and Brazil?

AFRICAN ORIGIN OF COMORIAN POPULATION



During their major migration, the Bantu people moved from west to east and continued towards the south around the year 1000 B.P.

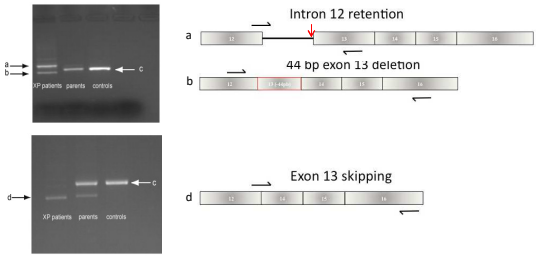
XP-C patients in Brazil with the same homozygous *XPC* mutation as in Comoros

- Family XP6 : mt DNA haplotype: L1b from central Africa for the mother and the father is from European origins (Portugal?)
- Family XP14: haplogroup R1b from sub-Saharian Africa for the father and the mother is from South Native American origin (haplogroup A).
- Family XP20: haplogroup J1b from Africa for the father and the mother is from South Native American origin (haplogroup D).

Collaboration Dr. Maria Isabel Achatz, Cancer Institute, Sao Paulo, Brazil

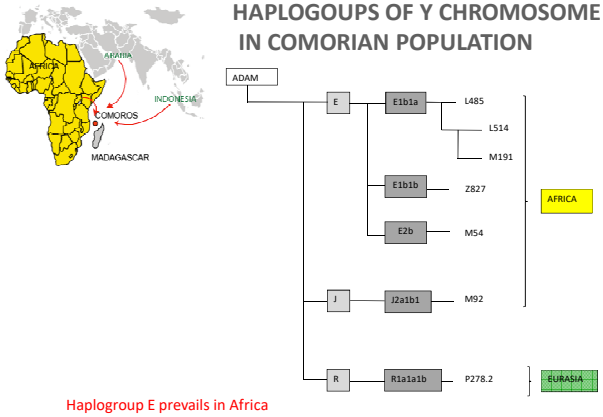
1-Description of the cohort of XP-C patients from Comorian islands

GENETIC CONSEQUENCES OF THE SPLICING MUTATION AT INTRON 12 IN COMORIAN XP-C



This new mutation abolishes a splice acceptor site leading to an aberrant splicing of *XPC* mRNA. 3 different *XPC* mRNA isoforms were found in XP-C cells

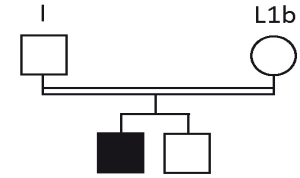
HAPLOGOUPS OF Y CHROMOSOME IN COMORIAN POPULATION



Haplogroup E prevails in Africa

Said Msaidie et al.,Eur J Hum Genet. 2011 January; 19(1): 89–94.

XP-C PATIENT FROM BRAZIL with the same mutation as in Comoros

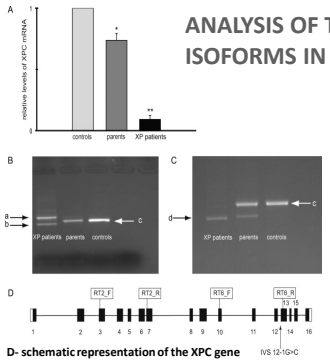


Y-markers I
mtDNA L1b

Family XP-C 6 of Maria Isabel Achatz (Sao Paulo, Brazil)

This family has a west-central African mt marker.

ANALYSIS OF THE *XP-C* mRNA ISOFORMS IN XP-C PATIENT'S CELLS



D- schematic representation of the XPC gene

A- The total amount of *XPC* mRNA is very low in XP-C patient's cells

B- PCR with primers RT6:
a - retention of intron 12
b - 44 deletion of exon 13

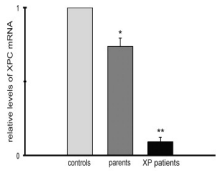
C-PCR with primers between exon 12-16:
d - exon 13 skipping

This new mutation abolishes a splice acceptor site leading to an aberrant splicing of XPC mRNA

COHORT DATA IN THE 18XP-C COMORIAN PATIENTS 12 MEN-6 WOMEN

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age of first symptom	7m	1m	?	6m	12m	2m	4m	7m	4m	8m	6m	8m	6m	9m	6m	11m	8m	8m
Ocular abnormalities	The first symptom was ocular in 83 % of cases																	
Photophoby	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Conjunctivitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Visual acuity	B	<S	B	>S	PL	PL	>S	>S	B	PL	?	<S	PL	>S	>S	>S	?	<S
Corneal opacity	+	+	+	-	-	+	-	+	+	+	?	-	-	+	-	-	-	+
Skin abnormalities	The first symptom was cutaneous 17 % of cases																	
Lentigines	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+
Xeroses	1	1	1	-	-	3	-	-	-	2	?	1	-	-	-	-	-	-
Skin atrophy	2	-	1	-	-	1	-	1	1	1	?	-	-	-	-	-	-	-
Hypopigmented patches	3	3	3	1	1	1	1	2	2	-	?	1	1	3	2	2	2	3
Hyperpigmented patches	3	3	1	1	2	3	2	3	3	3	?	1	2	3	2	2	2	3

GENETIC CONSEQUENCES OF THE SPLICING MUTATION AT INTRON 12 IN COMORIAN XP-C

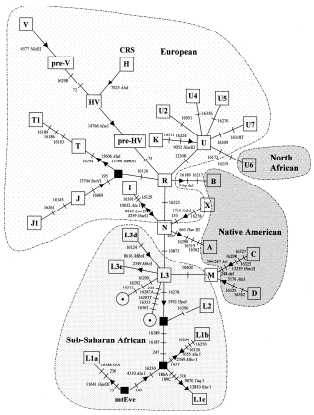


The total amount of *XPC* mRNA is very low in XP-C patient's cells

Classification tree for haplogroups present in the Brazilian population

Matrilineal contribution of white, middle-class Brazilian individuals:

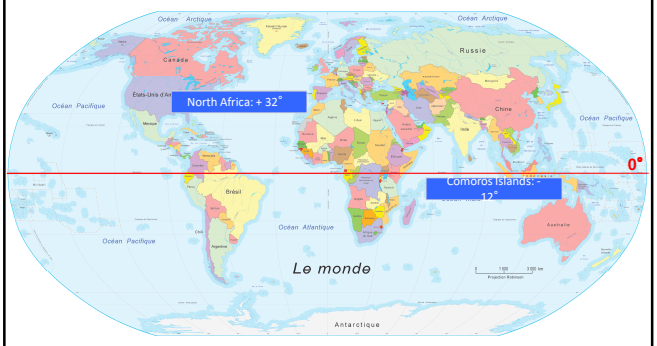
***33% native American**
***28% African**
***39% European (Portuguese males)**



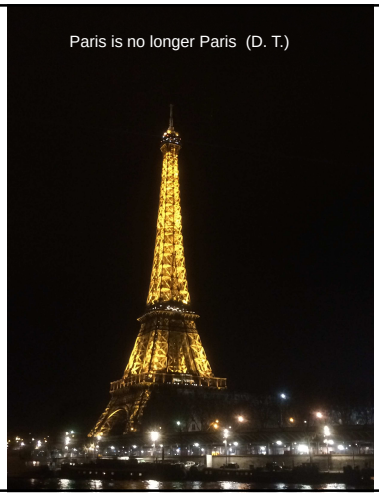
Alves-Silva et al., AJHG, 2000, 67, 444-461

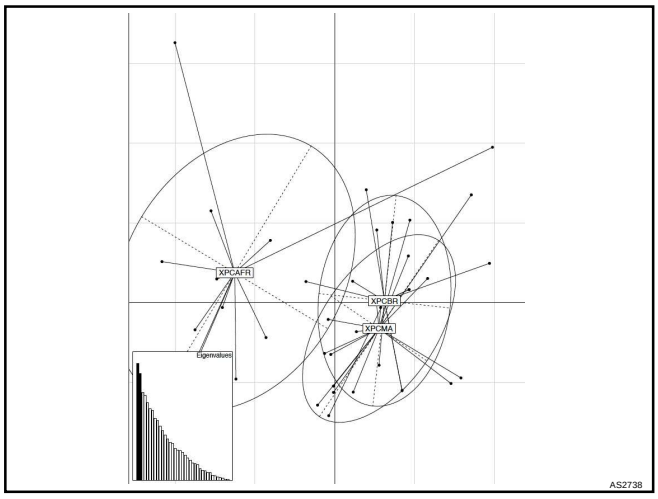
AS2719

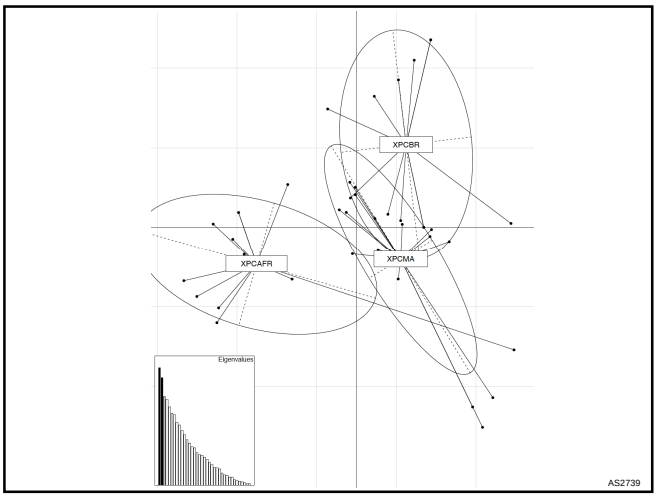
Comparison of XP-C symptoms between North Africa and Comorian Archipelago



AS2716




XPCAFR
XPCBR
XPCMA
Eigenvalues
AS2738


XPCBR
XPCAFR
XPCMA
Eigenvalues
AS2739

XP in Germany and European Reference Networks (ERN) Status quo and developments

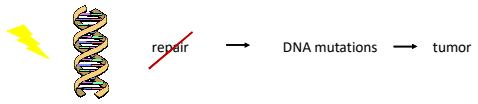
Monika Ettinger, MD.,Ph.D., University Hospital Regensburg, Dept. Dermatology

XP patients in Germany

- Center for rare (orphan) diseases
- Treatment and care of patients with DNA repair diseases
- Inpatient and outpatient clinic
- Molecular diagnosis
- Complementation group XP-C most common
- 50-60 XP patients
- Heterogeneous group with origins from Germany and northern Africa
- XP Freu(n)de support group

Xeroderma pigmentosum (XP)

- Autosomal recessive genetic disorder
- Incidence 1:10^6
- Defect in nucleotide excision repair
- No repair after ultraviolet (UV)-radiation induced damage (UVA > 320 nm, UVB 280-320 nm)



XP-case report

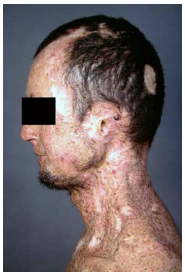
- 2 - year old boy
- Freckling with 8 months, swelling and persistent erythema after sun exposure
- In course of time mental and motor develomental delay

- **Gene analysis**: Stop mutation in *XPA* gene (homocygous) (c.545_546dupTA(p.Lys183*) (De Sanctis-Cacchione-syndrome)
- ***In vitro* analysis of repair capacity:** in progress

Xeroderma pigmentosum (XP)

- 8 complementation groups
  - (XP-A – XP-G) und XP-V

- Photosensitivity
- Freckling
- Persistent erythema
- Xerosis cutis
- Poikiloderma
- 30% progressive neurological degeneration
- 80% ophthalmological involvement
- 10 000-2000 fold risk skin cancer ↑



XP-case report

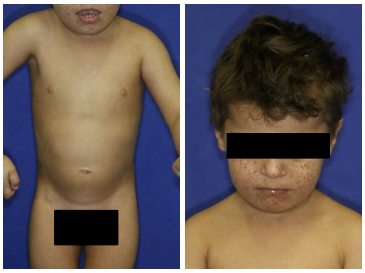
- **Scoring system to indicate severity**

- **Neurology:** Spasticity in both legs, increased tone, expanded cerebrospinal fluid space, starting brain volume reduction (XP score = 2)

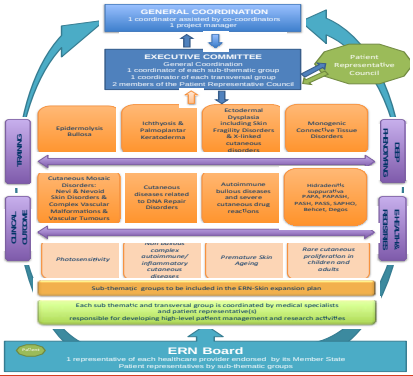
- **Ophthalmology:** clinically unremarkable (XP score = 0)

- **Dermatology:** (XP score = 2)

XP-case report



Structure of ERN skin



European Reference Network

for rare or low prevalence complex diseases

Network
Skin Disorders (ERN-Skin)

ERN-Skin Kick-Off Meeting 05/17 Brussels, Belgium

- 56 partners (18 countries, 8 + 4 subthematic groups, 4 transversal groups)
- 5 year goals
- Roles and responsibilities

European reference network (ERN)

- Virtual networks (virtual advisory panels)
- Help professionals and centers of expertise to share knowledge and harmonize procedures in countries
- Rare or low prevalence diseases requiring specialized care
- Ensure availability of treatment facilities

ERN skin participants

- Alain Taieb (rep Fanny Morice-Picard) (F)
- Mark Berneburg (G)
- Bob Sarkany (UK), Hiva Fassihi (UK)
- Smail Hadj-Rabia (F)
- Anna-Maria Ranki (Finland)
- Biagio Didona (I) Stefen Emmert (G), Hana Buckova (CZ),
- Juliette Mazereeuw (F), Kathrin Giel (G), Sally Ibbotson (UK),
- Celia Moss (UK)
- Patients support group representatives: XP-Freu(n)de (Germany),
- Ass Enfants de da lune (France)

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ERN-skin 5 year goals and activities

n°	Goals	Activities
1	Build a durable ERN SKIN involving the best experts and covering the largest possible number of diagnosed but also undiagnosed rare and low prevalence skin disorders so that every patient finds a home in the ERN-SKIN	Regular meetings, conference calls of the ERN SKIN leaders, of the ERN SKIN and overlapping ERNs and Scientific Societies Reports' dissemination
2	Provide reliable and harmonized information on diseases and services offered by each health care provider	Interactive directory with services provided by health care providers in and outside the ERN-SKIN
3	Develop multidisciplinary management	Guidelines and recommendations for patients and caregivers with scientific societies and other ERNs
4	Share and spread harmonized procedures and best practices within and outside of the ERN-SKIN	ERN SKIN website in close link with the ERN IT platform
5	Develop health care providers' skills in manage patient with rare skin diseases	Course, practical training, e-training for medics and paramedics within and outside the network for each sub thematic group of diseases
6	Empower patients and teach them how to manage their disease	Therapeutic education programs for children, adolescents and adults and or specific leaflets in collaboration with patient representatives
7	Facilitate the mobility of expertise and support healthcare providers to bring local, regional and national provision of care to patients closer to home to avoid unnecessary travel for patients and their families	Development of a teledermatology platform
8	Help Member States with insufficient number of patients or lacking technology or expertise to provide highly specialized services	Grants for training health care providers from Member States with an insufficient number of patients or lacking technology or expertise + Access to teledermatology Platform
9	Develop disease terminology among multidisciplinary team	SPOT app - Skin Phenotyping Ontology and Terminology Tools - Revised dermatologic terminology within the Human Phenotype Ontology
10	Develop research, epidemiological surveillance and pave the way for clinical trials	ERN-SKIN registry

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Participants and tasks

- Alain Taieb (rep Fanny Morice-Picard) (F): Chair, e-health and registry
- Mark Berneburg (G): co-chair, Research
- Bob Sarkany (UK): Guidelines
- Smail Hadj-Rabia (F): Clinical outcomes
- Anna-Maria Ranki (Finland) : Training
- Hiva Fassihi (UK): Deep phenotyping
- Maria Asuncion Vicente-Villa (ES): Therapeutic education
- Biagio Didona (I) Stefen Emmert (G, Research), Hana Buckova (CZ),
- Juliette Mazereeuw (F), Kathrin Giel (G), Sally Ibbotson (UK),
- Celia Moss (UK)
- Patients support group representatives: XP-Freu(n)de (Germany),
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ERN-Skin Meeting 11/17 Paris, France

- Discussion in subthematic groups
  - Determine main points and tasks

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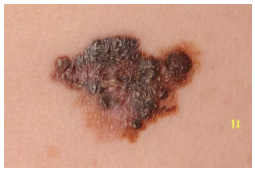
Malignant melanoma

- Develops from the pigment-containing cells known as melanocytes
- Primary cause of melanoma is ultraviolet light (UV) exposure



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Main points subthematic group DNA repair

Diagnostic technologies
- Listing of functional and molecular tools available for XP (exists)

Guidelines
- European guidelines (in process)
- Elaboration of a Skin Severity Scale (exists but will be expanded)

Registry
- Elaboration of a common ERN-skin registry including all the European patients (to be developed)
- Validation by all the members and by the board (to be done by every partner)

Research
- Listing of existing european research projects on Xeroderma Pigmentosum and other DNA repair diseases (under development)
- Development of Inhox clinical research project (Progelife)
- Discussion on possible collaborations/common projects (to be done)

Training
- Annual course on DNA repair disorders (to be done)

E-Health
- Telemedine, Skype…(Clinical patient management system CPMS)

Communication
- All the previous informations have to be found on a shared european website (to be developed)
- Regular meetings (has taken place 2x on webex)

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XP and skin tumors

- Mostly non-melanoma skin cancer (SCC, BCC)
- Less frequently malignant melanomas (MM)

Case report (Hauschild A et al. European J Cancer 02/17)

- 51-year old patient, complementation type E
- Since age 13 multiple skin tumors (SCCs, BCCs, MMs)
- Topical treatments, cryotherapy, photodynamic therapy, surgical removal
- Stage IV (pT1b, N2a, M1c)

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XP and skin tumors

- Interdisciplinary tumour board
  - Systemic treatment with the programmed cell death protein 1 (PD-1) antibody pembrolizumab
- 3-weekly injections (2mg/kg body weight)
- 3 months later
  - 90% decrease of the largest lung metastasis
  - Complete disappearance of small lung lesions
  - Almost all BCCs, AKs und Bowen's disease lesions disappeared
- Side effects: diffuse inflammation in areas of sun damaged skin

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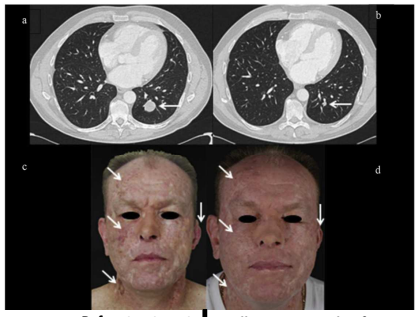
XP and skin tumors

- Melanomas are particularly immune-responsive
- BCC, SCC and Merkel cell carcinomas harbour even higher numbers of somatic mutations
- PD-1 antibodies (i.e. pembrolizumab) might represent effective systemic treatment and prevention of NMSC and melanoma

Regression of melanoma metastases and multiple non-melanoma skin cancers



Before treatment | **Follow up 6 months after**

Hauschild A; Europ J Cancer 77 84-87 (2017)

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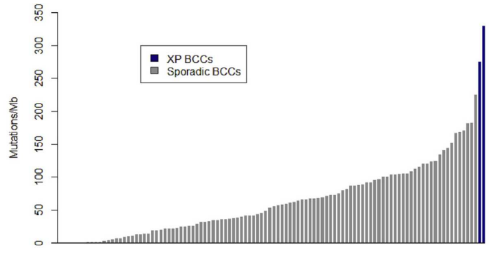
Summary

- Patients in Germany are a heterogeneous group with origins from Germany and northern Africa
- ERN: In addition to European XP-society, ERN is an important development and networking between countries will improve the situation of patients
- New treatments are available for patients with melanoma – as well as non melanoma skin cancer

Mutational burden of XP associated BCCs



Hauschild A, Weidinger S; Europ J Cancer 77 84-87 (2017)

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Thank you for your attention

Photosensitivity beyond the Skin

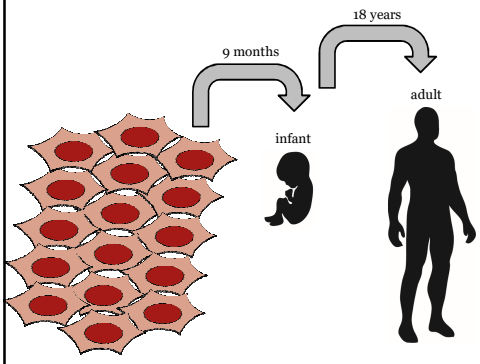
Department of Molecular Genetics

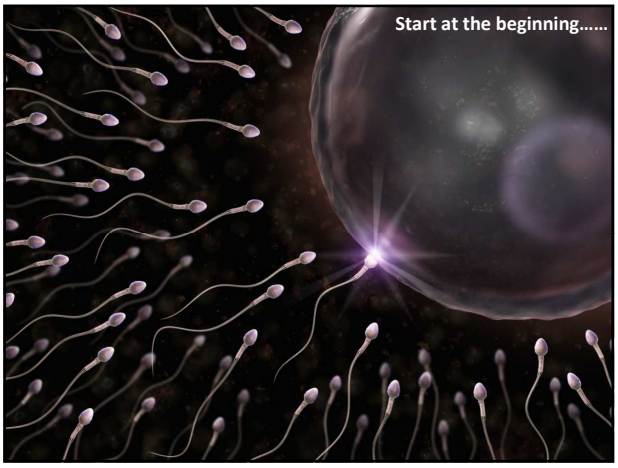
1st International XP Medical Conference, February 11, 2018, London

Erasmus MC

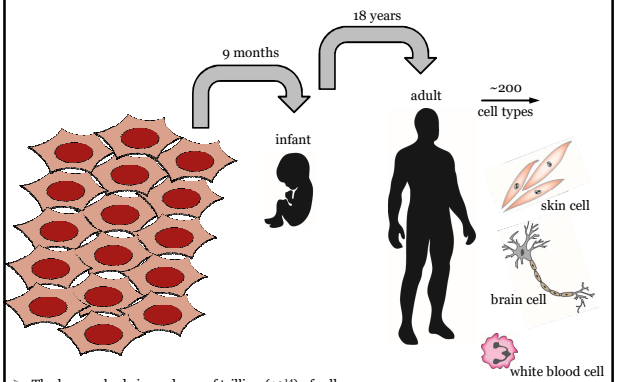
Arjan Theil
Dept. of Molecular Genetics, Erasmus University Medical Center Rotterdam, The Netherlands

The development of the human body



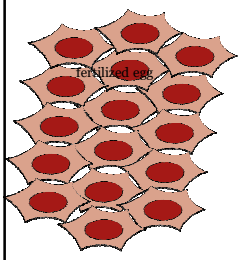


The development of the human body

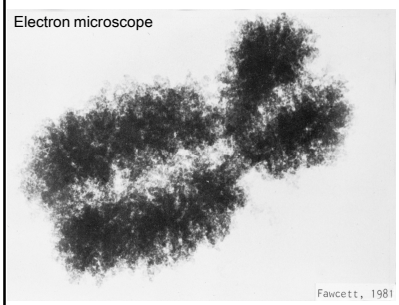


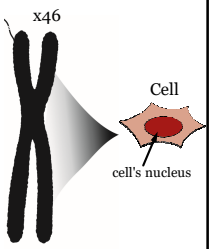
- The human body is made up of trillion (10^{14}) of cells

The development of the human body



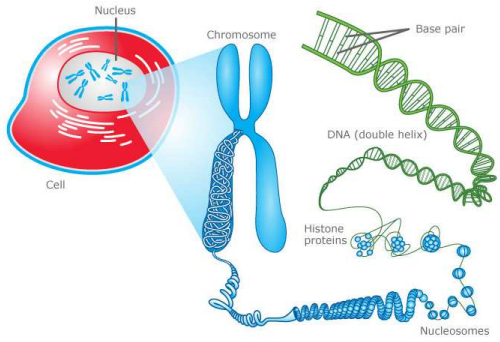
DNA is located in the cell's nucleus





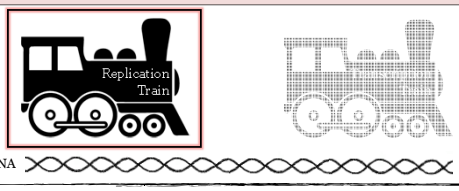
- Humans have 46 chromosomes

chromosome is a highly compressed form of DNA

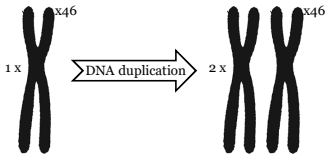


- A chromosome is DNA wrapped around protein complexes (e.g. histones)

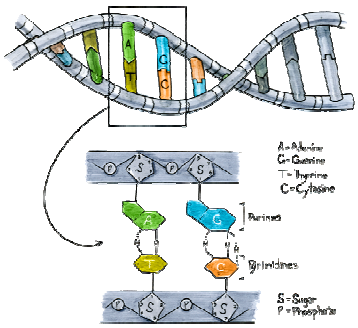
Replication "Train" duplicates entire DNA



Replication:

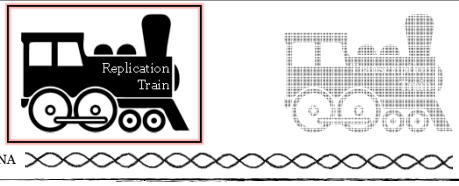


Building blocks of DNA

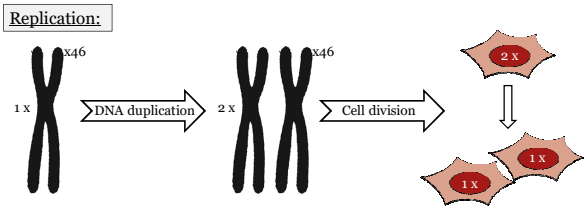


- DNA is a code that uses only 4 'letters': A, T, C en G (6 **billion** in humans)

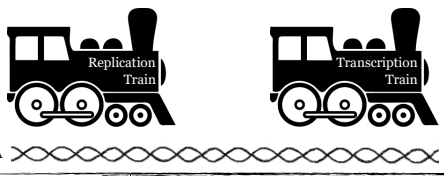
Replication "Train" duplicates entire DNA



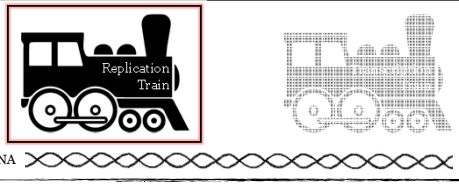
Replication:

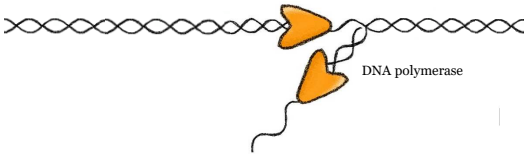


Processes that use the DNA "tracks"



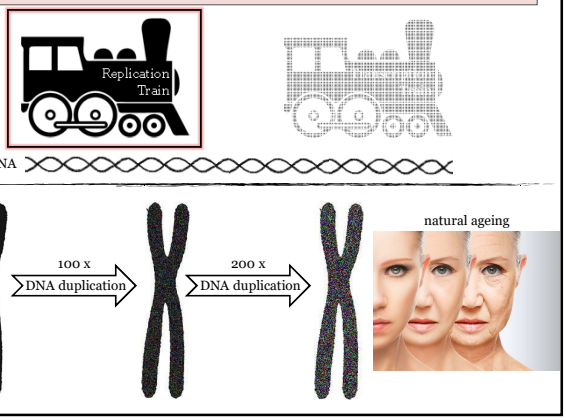
The Replication "Train" is called DNA polymerase



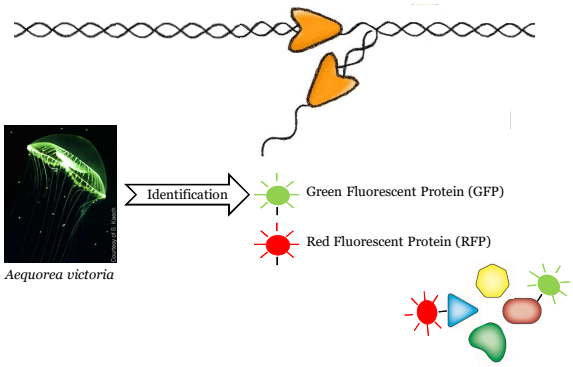


General rule: replication is a very accurate process (only 1 mistake in 9 billion letters)

Replication "Train" mistakes causes natural ageing

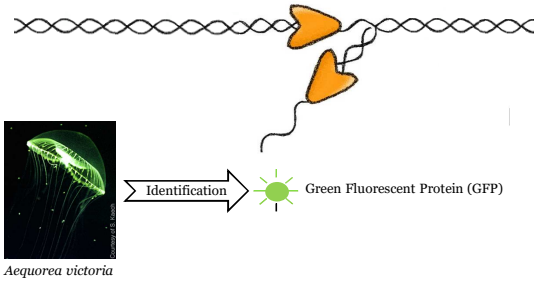


Visualize the Replication "Train"

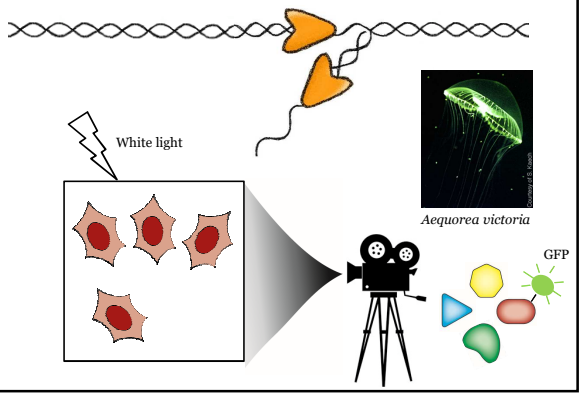


- Selectively force human cells to make a GFP-labeled proteins of interest in living cells

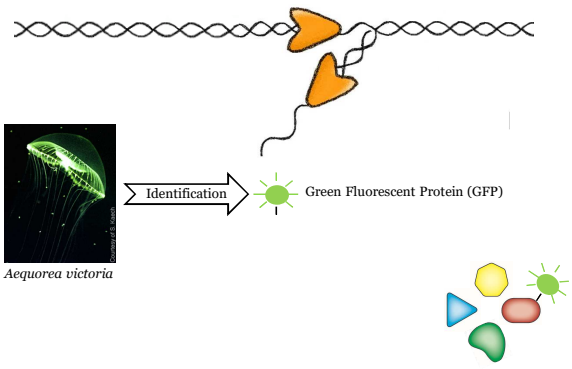
Visualize the Replication "Train"



Visualize the Replication "Train"

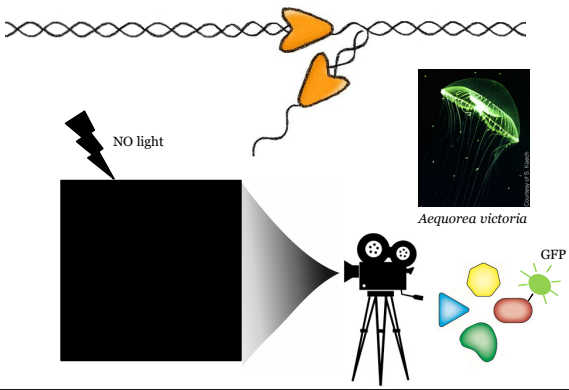


Visualize the Replication "Train"

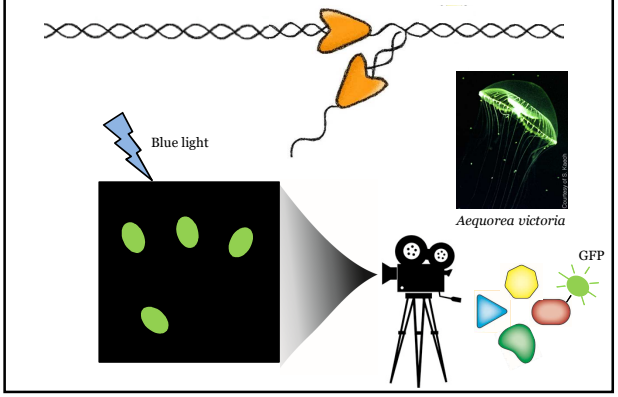


- Selectively force human cells to make a GFP-labeled version of your favourite protein

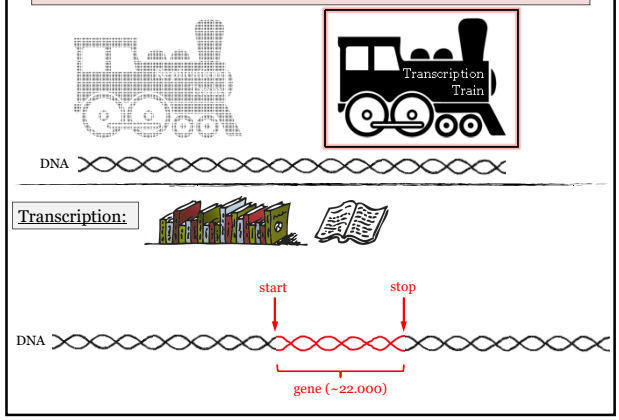
Visualize the Replication "Train"



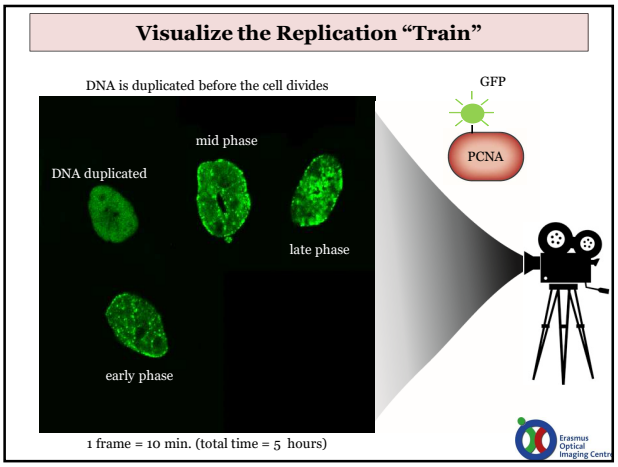
Visualize the Replication "Train"



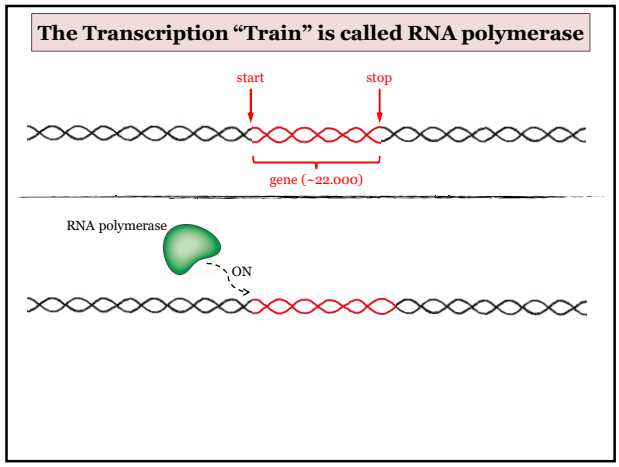
Genes contain instructions to make proteins



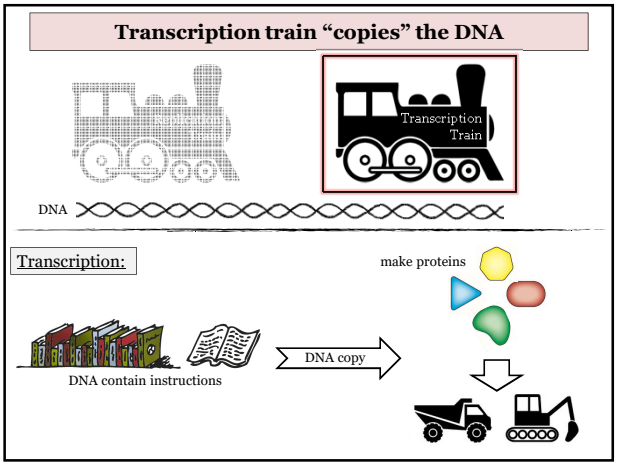
Visualize the Replication "Train"



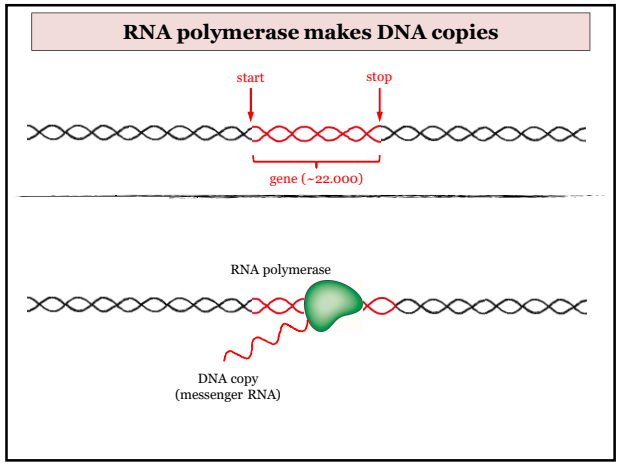
The Transcription "Train" is called RNA polymerase



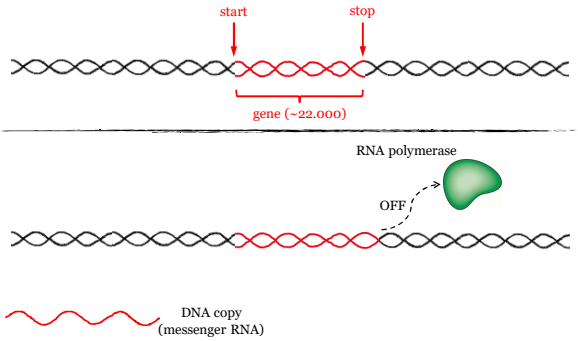
Transcription train "copies" the DNA



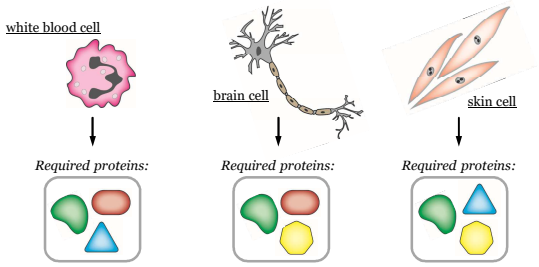
RNA polymerase makes DNA copies



RNA polymerase makes DNA copies

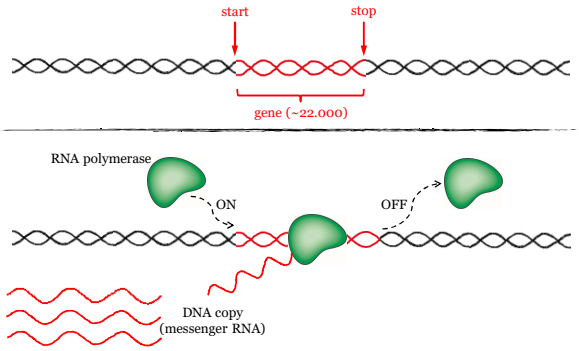


Not all genes are required



- Every cell has exactly the same DNA
- Not all information on the DNA is used → not all proteins are required
- Many genes are essential for every cell (housekeeping genes)
- Every cell type is unique and has their own set of proteins

RNA polymerase makes DNA copies



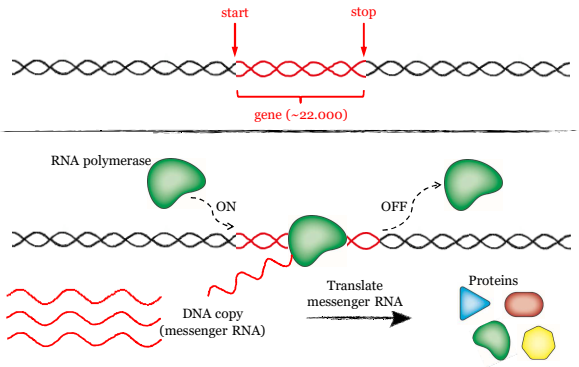
Not all genes are "ON"

RNA polymerase

The RNA polymerase **receives instructions**:
- Which gene is switch "ON" or "OFF"?
- How many copies?

Gene Regulatie

DNA copies are used to make proteins



General rule: Transcription is essential for life

Not all genes are "ON"

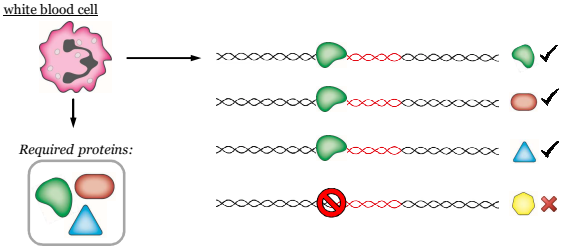
RNA polymerase

The RNA polymerase **receives instructions**:
- Which gene is switch "ON" or "OFF"?
- How many copies?

Gene Regulatie

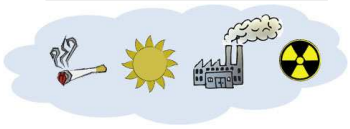
white blood cell

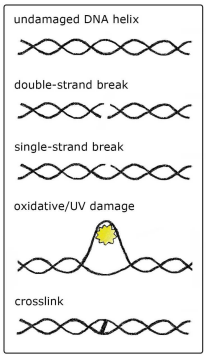
Required proteins:



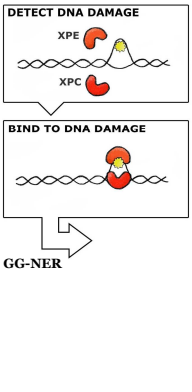
DNA is at risk!

DNA damage = ~100.000 per cell & per day





Global Genome NER (GG-NER)

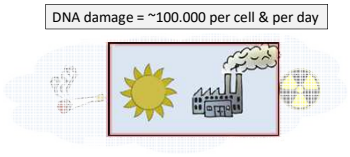


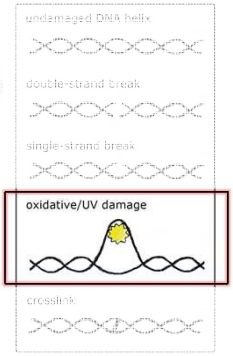
Global Genome Nucleotide Excision Repair (GG-NER):

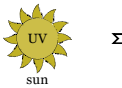
- Repairs DNA damage everywhere
- Prevents stalling of DNA polymerases
- Prevents stalling of RNA polymerases

DNA is at risk!

DNA damage = ~100.000 per cell & per day

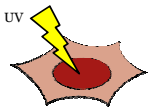






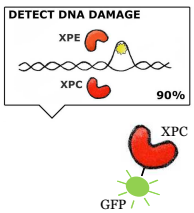
UV-induced DNA damage

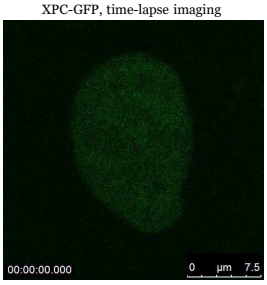
Visualize XPC accumulation at DNA damage



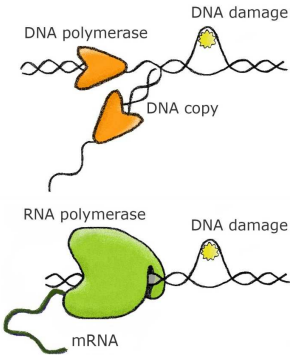
UV-C laser (266 nm) micro-beam irradiation to locally inflict DNA damage in cultured human cells.

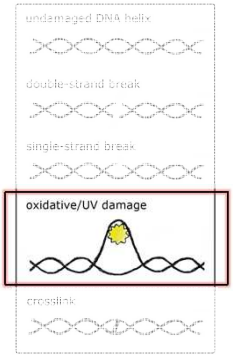
XPC-GFP, time-lapse imaging





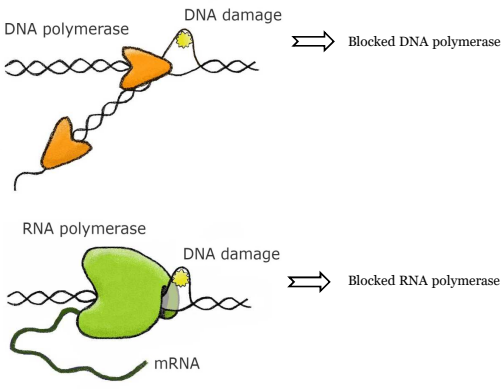
Replication & Transcription at risk!



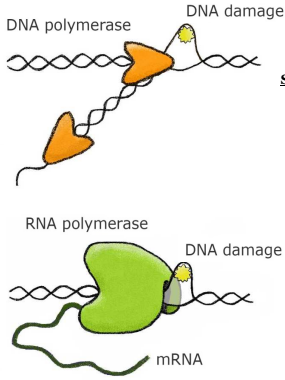


Nucleotide Excision Repair (NER) pathway repairs oxidative/UV-induced DNA damage

Blocked polymerases inhibit repair by GG-NER



Blocked polymerases inhibit repair by GG-NER



⇒ Blocked DNA polymerase

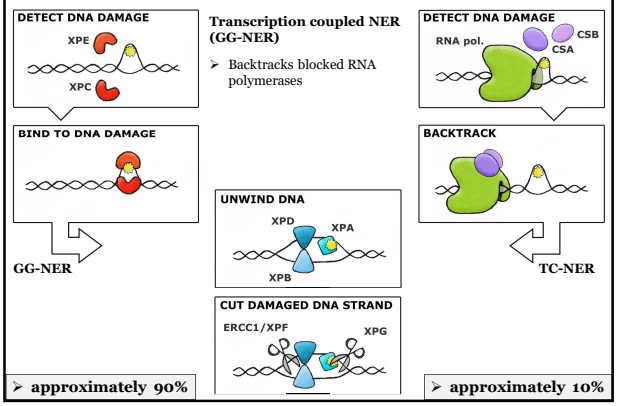
Solution = **ALTERNATIVE** DNA polymerase

Penalty = Alt. DNA polymerase is **FAULTY**

Result = increased mutations → **CANCER**

⇒ Blocked RNA polymerase

Transcription-Coupled NER (TC-NER)

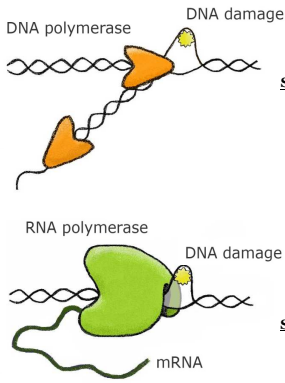


Transcription coupled NER (GG-NER)

- Backtracks blocked RNA polymerases

- approximately 90%
- approximately 10%

Blocked polymerases inhibit repair by GG-NER



⇒ Blocked DNA polymerase

Solution = **ALTERNATIVE** DNA polymerase

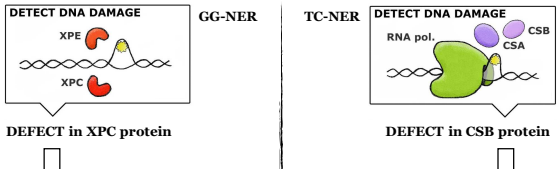
Penalty = Alt. DNA polymerase is **FAULTY**

Result = increased mutations → **CANCER**

⇒ Blocked RNA polymerase

Solution = Transcription-coupled NER (**TC-NER**)

Nucleotide Excision Repair (NER)



DEFECT in XPC protein → **Blocked DNA polymerases**

Solution = **ALTERNATIVE** DNA polymerase

Penalty = Alt. DNA polymerase is **FAULTY**

Result = increased mutations → **CANCER**

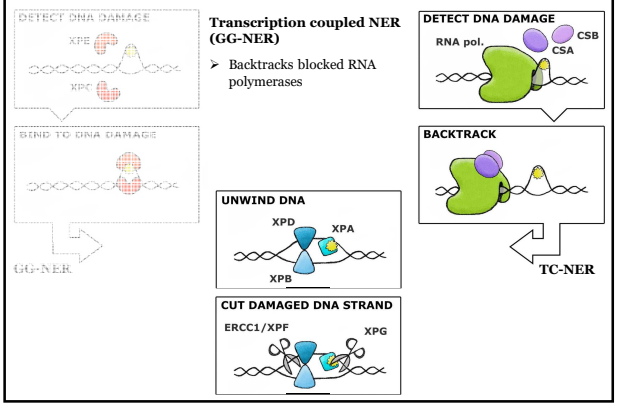
DEFECT in CSB protein → **Blocked RNA polymerases**

Solution = **NO BYPASS** possible

Penalty = **DISTURBED TRANSCRIPTION**

Result = increased cell death → **AGEING**

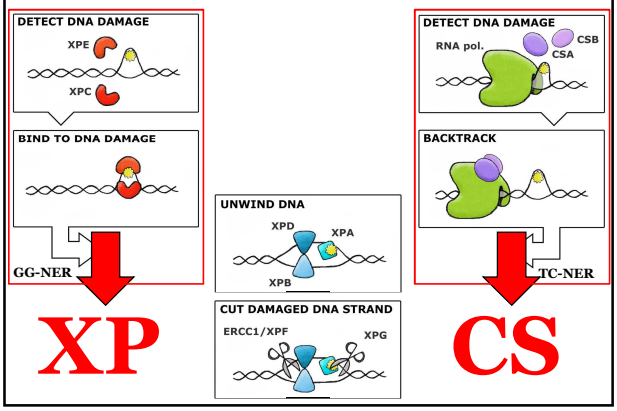
Transcription-Coupled NER (TC-NER)



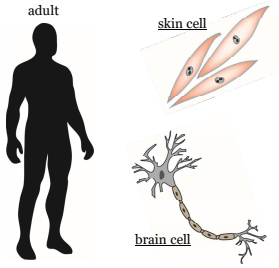
Transcription coupled NER (GG-NER)

- Backtracks blocked RNA polymerases

Nucleotide Excision Repair (NER)

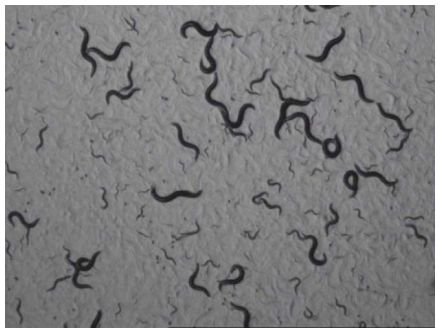


Disclaimer: majority of cells do not divide anymore



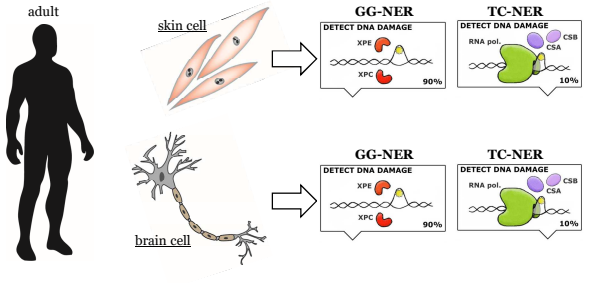
- **dividing cells**
  e.g. skin cells, intestine cells, white blood cells
- **non-dividing cells**
  e.g. brain cells, muscle cells, photoreceptor cells eye

C. elegans as model organism to study NER

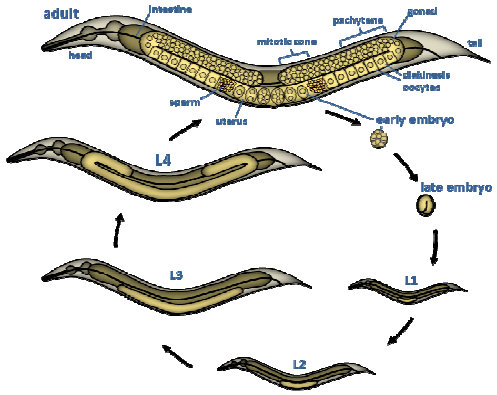


- *C. elegans* is a is transparent nematode (roundworm), about 1 mm in length that lives in soil environments.
- *C. elegans* is used in our laboratory to study DNA repair mechanisms

Disclaimer: majority of cells do not divide anymore



C. elegans as model organism to study NER



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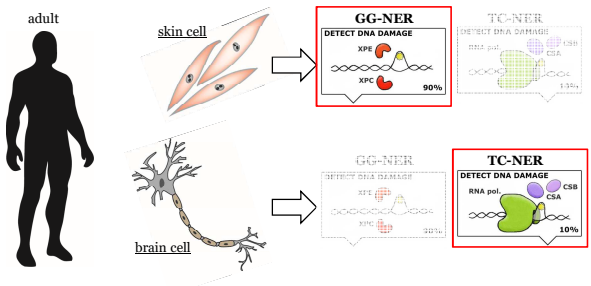
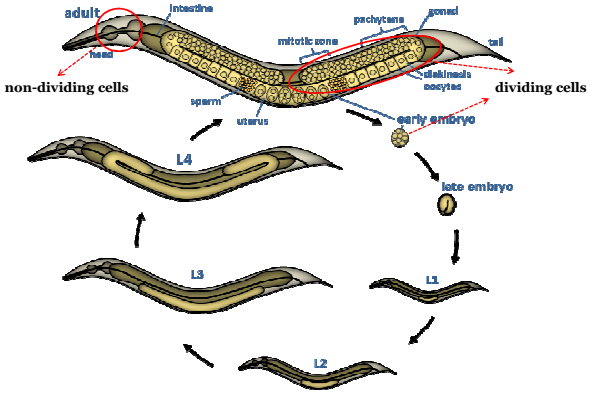
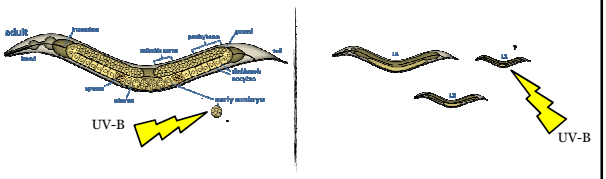


- Dividing cells mainly depend on GG-NER
- Non-dividing cells mainly depend on TC-NER

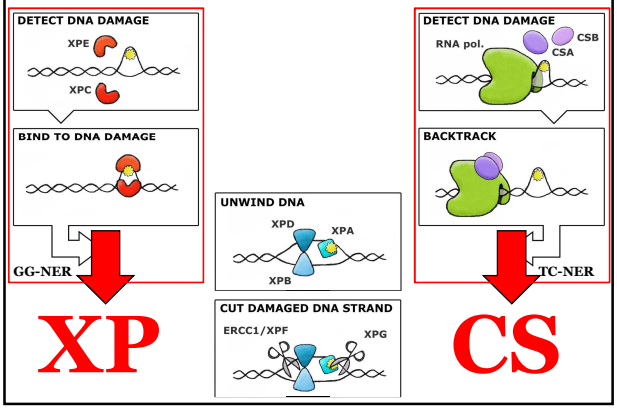
C. elegans as model organism to study NER



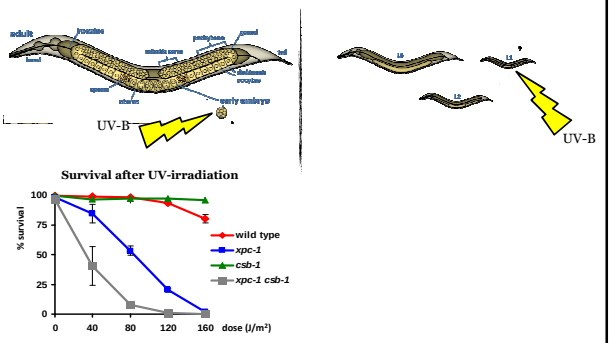
C. elegans to study human repair disease



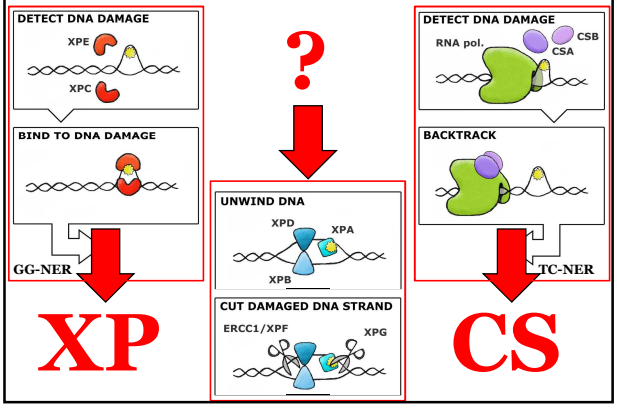
Nucleotide Excision Repair (NER)



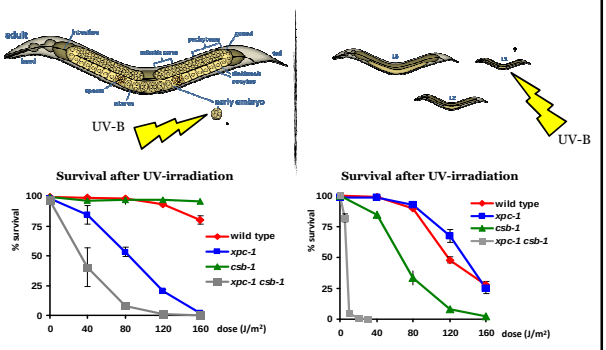
C. elegans to study human repair disease



Nucleotide Excision Repair (NER)



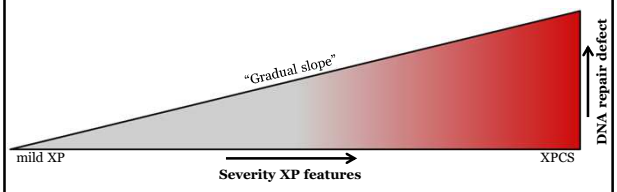
C. elegans to study human repair disease



- GG-NER protects dividing cells from blocked replication (early embryo)
- TC-NER protects non-dividing cells from blocked transcription (young adult worm)

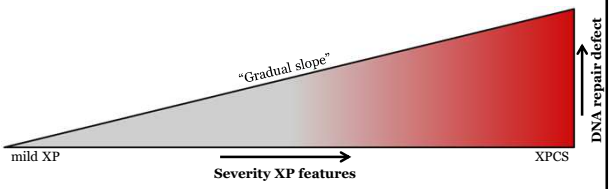
Severity of XP features

Hypothesis: severity of clinical features is a "gradual slope"



Severity of XP features

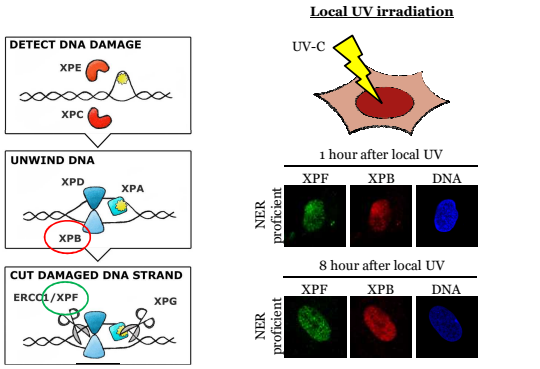
Hypothesis: severity of clinical features is a "gradual slope"



mild XP = i.e. UV-light sensitive, no neurological problems, no developmental problems

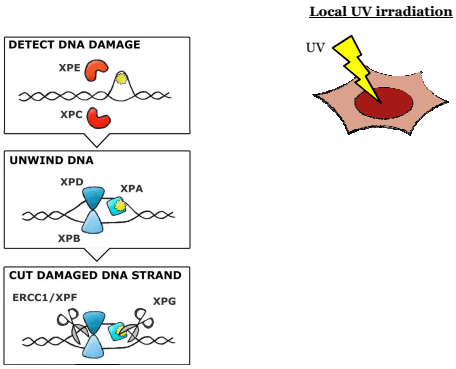
XPCS = i.e. UV-light sensitive, neurological problems, developmental problems, premature ageing

Local UV Damage & Repair Kinetics in Human Cells

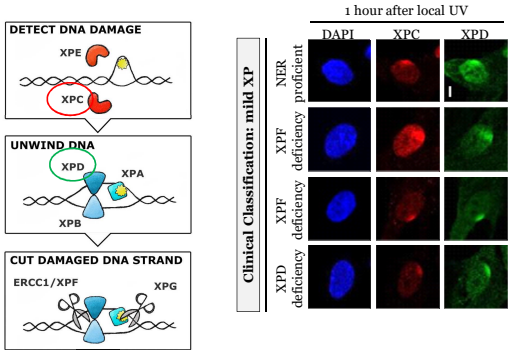


- Most DNA damage is repaired by NER after 8 hours

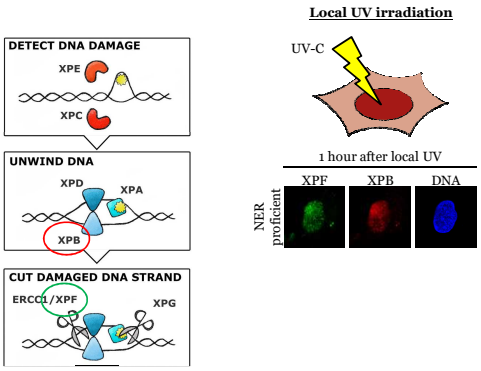
Local UV Damage & Repair Kinetics in Human Cells



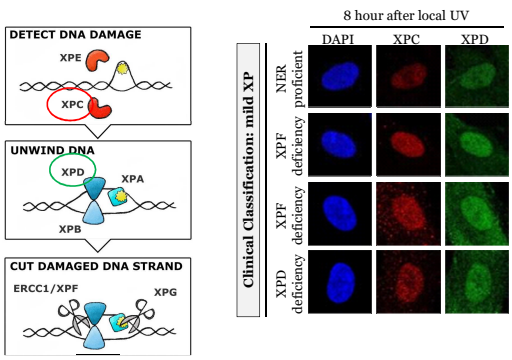
DNA Repair capacity is mildly affected in XP cells



Local UV Damage & Repair Kinetics in Human Cells

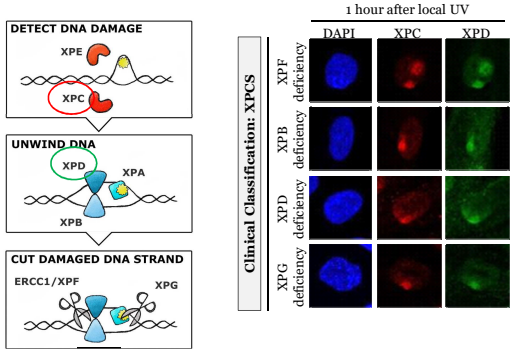


DNA Repair capacity is mildly affected in XP cells

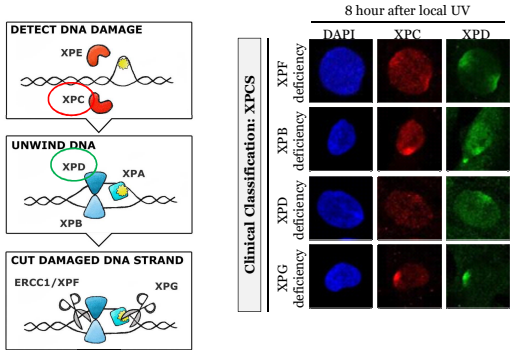


- Mild XP cells still have some NER activity

DNA Repair capacity is severely affected in XPCS cells



DNA Repair capacity is severely affected in XPCS cells



- Severe XPCS cells have severely reduced NER capacity

Future prospective

- How to predict the severity of XP symptoms based on mutation
- How blocked transcription machines alter the cell's metabolism (cell's energy regulation)

cell's metabolism

Mouse experiments → Food consumption is important:
- eat healthy
- not too much food

- Discovery of a novel gene editing technique for scientific research (CRISPR-Cas9 technology)