CLINICAL, MOLECULAR, AND EPIDEMIOLOGIC STUDIES OF XERODERMA PIGMENTOSUM AND RELATED DISORDERS OF DNA REPAIR

Kenneth H. Kraemer, M.D.
Chief, DNA Repair Section
Basic Research Laboratory
Center for Cancer Research
National Cancer Institute, Bethesda, MD
• CLINICAL FEATURES OF DNA REPAIR DISORDERS
• MOLECULAR ABNORMALITIES IN XERODERMA PIGMENTOSUM PATIENTS
• EPIDEMIOLOGICAL STUDIES OF XP GENE POLYMORPHISMS AND XP FAMILIES
• CLINICAL FEATURES OF DNA REPAIR DISORDERS
• MOLECULAR ABNORMALITIES IN XERODERMA PIGMENTOSUM PATIENTS
• EPIDEMIOLOGICAL STUDIES OF XP GENE POLYMORPHISMS AND XP FAMILIES
MORITZ KAPOSI

First description of XP patients - 1870

Moriz Kohn 1837 - 1902
AFRICAN AMERICAN WITH XERODERMA PIGMENTOSUM

SCC FACE

SCC TONGUE
XERODERMA PIGMENTOSUM

Autosomal recessive
Clinical sun sensitivity, marked freckling
SKIN CANCERS (BCC, SCC, Melanoma)

Cellular UV hypersensitivity
Defective DNA repair
7 nucleotide excision repair complementation groups
(XPA, XPB, XPC, XPD, XPE, XPF, XPG)
VARIANT with normal NER – defective bypass polymerase

Chromosomes: 9q34 (A), 2q21 (B), 3p25.1 (C), 19q13.2 (D),
11p12-p11 (E), 16p13.3 (F), 13q33 (G), 6p21.1 (Variant)
Cloned genes XPA, XPB (ERCC3), XPC, XPD (ERCC2),
XPE (DDB2), XPF (ERCC4), XPG (ERCC5), Variant (POLH)
XP Features

• Equally distributed among males and females
• Ethnicity:
  • Middle East
  • Europe
  • Japan
  • Africa
  • America
• Frequency: 1:100,000 in Japan
• Frequency: 1:1,000,000 in U.S.
• Oldest patient: 85 yr
• Sun sensitivity or freckling (median age of onset): 1.5 yr
• Skin cancer (median age of onset): 8 yr
• 97% of basal & squamous cells carcinoma occur on face, head, or neck
• 65% of melanomas occur on face, head, or neck
• In the past, death occurred 30 yr earlier than in the US general pop.
• Sun protection may prolong life.
EARLY AGE OF ONSET OF SKIN CANCER IN XP

Arch Dermatol 123:241, 1987
# ELEVATED CANCER FREQUENCY IN XERODERMA PIGMENTOSUM

## Table 1. Frequencies of Skin, Eye, Tongue, and Internal Cancers in Patients With Xeroderma Pigmentosum (XP) Compared With the US General Population

<table>
<thead>
<tr>
<th>Cancer Sites</th>
<th>Age, y</th>
<th>No. of XP Patients</th>
<th>No. of XP Patients With Cancer</th>
<th>Ratio: Observed/Expected</th>
<th>95% C.I.‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Expected*</td>
<td>Observed†</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sun-Exposed Sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin basal cell and squamous cell carcinomas</td>
<td>0-19</td>
<td>77</td>
<td>0.01</td>
<td>49</td>
<td>4900</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.13</td>
<td>52</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.51</td>
<td>76</td>
<td>150</td>
</tr>
<tr>
<td>Skin melanomas</td>
<td>0-19</td>
<td>77</td>
<td>0.001</td>
<td>8</td>
<td>8000</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.022</td>
<td>14</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.042</td>
<td>29</td>
<td>700</td>
</tr>
<tr>
<td>Eye cancers</td>
<td>0-19</td>
<td>77</td>
<td>0.004</td>
<td>4</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.007</td>
<td>5</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.009</td>
<td>15</td>
<td>1700</td>
</tr>
<tr>
<td>Tongue cancers</td>
<td>0-19</td>
<td>77</td>
<td>0.00003</td>
<td>3</td>
<td>100 000</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.001</td>
<td>3</td>
<td>3000</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.004</td>
<td>3</td>
<td>800</td>
</tr>
<tr>
<td><strong>Sun-Shielded Sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All internal cancers§</td>
<td>0-19</td>
<td>77</td>
<td>0.09</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.36</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.81</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Brain and other central nervous system</td>
<td>0-19</td>
<td>77</td>
<td>0.02</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>0-39</td>
<td>123</td>
<td>0.05</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>All (0-62)</td>
<td>132</td>
<td>0.06</td>
<td>2#</td>
<td>33</td>
</tr>
</tbody>
</table>

*Calculated from cumulative age-specific annual rates of basal cell and squamous cell carcinoma from Scotto et al.; others from Young et al.*

†Age at first neoplasm of indicated type.

‡95% confidence interval based on the Poisson distribution.

§Including brain and other central nervous system but excluding melanoma of the eye, lip, and tongue.

||Brain sarcoma, 18-year-old patient; spinal cord astrocytoma, 24-year-old patient; lung carcinoma, 34-year-old smoker; gastric cancer, 50-year-old patient

#Brain sarcoma, 16-year-old patient; spinal cord astrocytoma, 24-year-old patient (same cases listed above).

Arch Dermatol 130:1018, 1994
X-RAY HYPERSENSITIVITY IN Basal Cell Nevus Syndrome BUT NOT IN XP!

X-Ray Treatment of BCC in Basal Cell Nevus Syndrome
Multiple skin cancers in site of treatment

X-Ray Treatment of Spinal Cord Astrocytoma in XP
Normal response to treatment.
SUN PROTECTION WITH NASA SUIT IN XP

4 y/o
XERODERMA PIGMENTOSUM GROUP G

Marked sun sensitivity in childhood

14 y/o – well protected
minimal skin changes

J Invest Dermatol 118: 972-82, 2002
ORAL ISOTRETINOIN PREVENTS NEW SKIN CANCERS IN XERODERMA PIGMENTOSUM

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

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

SIDE EFFECTS OF ORAL ISOTRETINOIN FOR XERODERMA PIGMENTOSUM

Kraemer et al NEJM 315: 1615 (1986)

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

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>NO. OF PATIENTS AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin</td>
<td>7</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>7</td>
</tr>
<tr>
<td>Blepharitis or Conjunctivitis</td>
<td>7</td>
</tr>
<tr>
<td>Lightening or disappearance of freckles</td>
<td>6</td>
</tr>
<tr>
<td>Increased serum triglycerides</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal liver-function tests</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcal infection (perioral)</td>
<td>3</td>
</tr>
<tr>
<td>Multiple pyogenic granulomas</td>
<td>2</td>
</tr>
<tr>
<td>Skeletal toxicity</td>
<td>2</td>
</tr>
</tbody>
</table>
XERODERMA PIGMENTOSUM with NEUROLOGICAL ABNORMALITIES

Autosomal recessive
Usually blistering on minimal sun exposure, Marked freckling
SKIN CANCERS (BCC, SCC, Melanoma)
Progressive neurological degeneration (20% of XP)
Primary neuronal degeneration
Progressive sensorineural deafness

Cellular UV hypersensitivity
Defective DNA repair
4+ nucleotide excision repair complementation groups
(XPA, XPB, XPD, XPG, rarely XPC)

Chromosomes: 9q34 (A), 2q21 (B), 3p25.1 (C), 19q13.2 (D), 13q33 (G)
Cloned genes XPA, XPB (ERCC3), XPC, XPD (ERCC2), XPG (ERCC5)
XERODERMA PIGMENTOSUM WITH NEUROLOGICAL ABNORMALITIES

XP12BE - XPA  XP11BE - XPB/CS  XP6BE - XPD

Annals Internal Med 80: 221-248, 1974
COCKAYNE SYNDROME

Autosomal recessive
Clinical sun sensitivity
Progressive neurological degeneration
Abnormal myelination of brain
Deafness, dwarfism, retinopathy

NO CANCER

Cellular UV hypersensitivity
Defective repair of actively transcribed genes
(defective TC-NER)
Defective repair of cyclobutane dimers
Normal repair of 6-4 UV photoproducts

2 Complementation groups (CSA, CSB)
Chromosome: 5 (CSA), 10q11 (CSB)
Cloned genes: CSA (ERCC8), CSB (ERCC6)
Cockayne Syndrome

Calcification in Basal Ganglia

3 y/o
XERODERMA PIGMENTOSUM / COCKAYNE SYNDROME COMPLEX

Neurological and somatic features of CS with Skin and cellular abnormalities of XP

SKIN CANCER

Cellular UV hypersensitivity
Defective DNA repair
3 XP complementation groups (XPB, XPD, XPG)

Chromosomes: 2q21 (B), 19q13.2 (D), 13q33 (G)
Cloned genes: XPB (ERCC3), XPD (ERCC2), XPG (ERCC5)
XERODERMA PIGMENTOSUM /
COCKAYNE SYNDROME COMPLEX

XP/CS group B - XP11BE
28 y/o  Mother
Annals Internal Med 80: 221-248, 1974
TRICHOTHIODYSTROPHY

Autosomal recessive
Photosensitive, Ichthyosis
Sulfur deficient Brittle hair
Intellectual impairment, Decreased fertility
Short stature (PIBIDS)

NO CANCER

Cellular UV hypersensitivity
Defective DNA Repair
3 complementation groups (XPB, XPD, TTDA)

Chromosome: 2q21 (XPB), 19q13.2 (XPD)
Cloned genes: XPB (ERCC3), XPD (ERCC2), TTDA (GTF2H5)
• CLINICAL FEATURES OF DNA REPAIR DISORDERS
• MOLECULAR ABNORMALITIES IN XERODERMA PIGMENTOSUM PATIENTS
• EPIDEMIOLOGICAL STUDIES OF XP GENE POLYMORPHISMS AND XP FAMILIES
DNA REPAIR –
THE LIFEGUARD OF THE GENE POOL
UV HYPERSENSITIVITY OF XP AND CS CELLS
UV PHOTOPRODUCTS

adjacent pyrimidines

cyclobutane pyrimidine dimer (CPD)

NUCLEOTIDE EXCISION REPAIR

Van Steeg & Kraemer
Mol Med Today 5; 86-94, 1999
• CLINICAL FEATURES OF DNA REPAIR DISORDERS
• MOLECULAR ABNORMALITIES IN XERODERMA PIGMENTOSUM PATIENTS
• EPIDEMIOLOGICAL STUDIES OF XP GENE POLYMORPHISMS AND XP FAMILIES
DNA REPAIR GENES AND CANCER RISK

Disease gene homozygotes
- low frequency
- known function
- very high cancer risk

Polymorphisms in the general population
- frequency > 1%
- unknown function
- unknown cancer risk

Disease gene heterozygote
- mid frequency
- known function
- unknown cancer risk
TURKISH XP PATIENTS

XP67TMA 7 y/o

XP68TMA 5 y/o

XP FAMILY FROM VAN, TURKEY

ASSIGNMENT OF XP67TMA and XP68TMA to XP COMPLEMENTATION GROUP C

![Graph showing CAT-Activity (%)](image)

- **CAT-Activity (%)** on the y-axis
- **UV-C Dose (J/m²)** on the x-axis

Legend:
- XP67MA+pEBS7
- XP67MA+pXPC
- XP68MA+pEBS7
- XP68MA+pXPC

JID 117:197, 2001
MOLECULAR ANALYSIS OF XPC cDNA IN XP67TMA

C1840T
Arg 579 Stop

J Invest Dermatol
117:197, 2001
# GENETIC ANALYSIS OF XP-C FAMILIES IN TURKEY AND ITALY

Molecular genetic analysis of XPC alleles and flanking markers

<table>
<thead>
<tr>
<th>Genethon (cM)</th>
<th>Microsatellite Marker</th>
<th>Turkish Alleles</th>
<th>Italian Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symbol</td>
<td>Paternal</td>
<td>Maternal</td>
</tr>
<tr>
<td>0</td>
<td>D3S1270(+</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1.4</td>
<td>D3S1307(+)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2.5</td>
<td>D3S1297(+)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>D3S1515(+</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>16.5</td>
<td>D3S1304(+</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24.1</td>
<td>D3S1597</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>30.9</td>
<td>D3S1263</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30.9</td>
<td>D3S1259</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>M3-NT_022498-B14544</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>D3S1585</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>XPC</td>
<td>C1840T ARG579STOP</td>
<td>stop</td>
<td>stop</td>
</tr>
<tr>
<td>XPC</td>
<td>T1601C VAL499ALA</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>XPC</td>
<td>A2920C LYS939GLU</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>M3-NT_005681-B2763</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>M3-NT_005681-B84724</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>36.8</td>
<td>D3S3726</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>35.7</td>
<td>D3S1554</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>M3-NT_005681-B20725</td>
<td>stop</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>36.9</td>
<td>D3S1293</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>46.8</td>
<td>D3S1283</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>46.8</td>
<td>D3S1266</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>50.4</td>
<td>D3S3727</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Large regions of identity indicate close (recent) relationships.

Smaller regions of identity indicate distant (older) relationships.

DETERMINATION OF GENETIC RELATIONSHIPS USING MICROSATELLITE MARKERS

\[ R = 1 - e^{(-g\theta)} \]

(Luria and Delbruck, 1943) where

- \( R \) is the proportion of chromosomes with recombination
- \( g \) is the number of generations
- \( \theta \) is the genetic distance between recombined markers

Turkish parents: \( R = 0.5 \quad \theta = 0.159 \quad g = 4 \) generations

Italian parents: \( R = 0.5 \quad \theta = 0.06 \quad g = 12 \) generations

Assuming 1 generation is 20 years then this analysis suggests a common ancestor about 300-500 years ago.

DETERMINATION OF GENETIC RELATIONSHIPS USING MICROSATELLITE MARKERS

\[ R = 1 - e^{-g\theta} \]

(Luria and Delbruck, 1943) where

- \( R \) is the proportion of chromosomes with recombination
- \( g \) is the number of generations
- \( \theta \) is the genetic distance between recombined markers

Turkish parents: \( R = 0.5 \)  \( \theta = 0.159 \)  \( g = 4 \) generations

Italian parents: \( R = 0.5 \)  \( \theta = 0.06 \)  \( g = 12 \) generations

Both families: \( R = 0.5 \)  \( \theta = 0.048 - 0.027 \)  \( g = 14-26 \) generations

Assuming 1 generation is 20 years then this analysis suggests a common ancestor about 300-500 years ago.

XPC MUTATION MIGRATION BETWEEN BOLOGNA, ITALY and VAN, TURKEY 300-500 years ago

~ 2000 miles
DNA REPAIR GENES AND CANCER RISK

Disease gene homozygotes
- low frequency
- known function
- very high cancer risk

Polymorphisms in the general population
- frequency > 1%
- unknown function
- unknown cancer risk
XPC SPLICE ACCEPTOR POLYMORPHISM

<table>
<thead>
<tr>
<th>NIH donors</th>
<th>Genotype distribution observed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
</tr>
<tr>
<td>p^2</td>
<td>2pq</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>100%</td>
</tr>
<tr>
<td>37</td>
<td>38%</td>
</tr>
<tr>
<td>38</td>
<td>39%</td>
</tr>
<tr>
<td>22</td>
<td>23%</td>
</tr>
</tbody>
</table>

Nucleic Acids Research 30: 3624, 2002
RELATIONSHIP OF XPC INTRON 11 GENOTYPE TO ABNORMAL SPLICING AND REDUCED DNA REPAIR FUNCTION

Nucleic Acids Research 30: 3624, 2002
XPC PAT+ ALLELE IS A MARKER OF INCREASED RISK OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

<table>
<thead>
<tr>
<th>CASES</th>
<th>CONTROLS</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL NUMBER</td>
<td>287</td>
<td>311</td>
</tr>
<tr>
<td>PAT + ALLELE FREQUENCY</td>
<td>0.409</td>
<td>0.333</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAT GENOTYPE</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>ADJUSTED ODDS RATIO</th>
<th>TREND TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>(95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>-/-</td>
<td>102</td>
<td>141</td>
<td>1.00 (1.01-2.05)</td>
<td>0.007</td>
</tr>
<tr>
<td>(35.6)</td>
<td>(45.3)</td>
<td>(45.3)</td>
<td>(35.6) (47.0)</td>
<td>(17.4) (42.8)</td>
</tr>
<tr>
<td>+/-</td>
<td>135</td>
<td>133</td>
<td>1.44 (1.12-3.05)</td>
<td></td>
</tr>
<tr>
<td>(+/+)</td>
<td>50</td>
<td>37</td>
<td>1.85 (1.12-3.05)</td>
<td></td>
</tr>
<tr>
<td>(+/+</td>
<td>1.00</td>
<td>1.44</td>
<td>1.85 (1.12-3.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.00 (1.01-2.05)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.44 (1.12-3.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.85 (1.12-3.05)</td>
<td></td>
</tr>
</tbody>
</table>

Cancer Res. 61:3321 (2001)
DNA REPAIR GENES AND CANCER RISK

Disease gene homozygotes
- low frequency
- known function
- very high cancer risk

Polymorphisms in the general population
- frequency > 1%
- unknown function
- unknown cancer risk

Disease gene heterozygote
- intermediate frequency
- known function
- unknown cancer risk
XP HETEROZYGOTES ARE MUCH MORE FREQUENT THAN HOMOZYGOTES

Hardy Weinberg equilibrium

$$X^2 + 2Xy + y^2$$

In US:
XP DISEASE FREQ ($y^2$) = ABOUT $10^{-6}$
then $y = 10^{-3}$
NORMAL ($X^2$) = 1 - $y^2$ or about 1
Heterozygotes ($2Xy$) = 2/1000 or 1/500

In Japan:
XP DISEASE FREQ ($y^2$) = ABOUT $10^{-5}$
then $y = 0.003$
NORMAL ($X^2$) = 1 - $y^2$ or about 1
Heterozygotes ($2Xy$) = 6/1000 or 1/158
DO XP HETEROZYGOTES HAVE INCREASED CANCER RISK?

• Swift, M and Chase, C. Cancer in Families with Xeroderma Pigmentosum JNCI 62:1415, 1979
• Studied 31 families - 2597 blood relatives and spouse controls
• Nonmelanoma skin cancer: 30/1046 blood rel vs 11/855 spouses p=0.02 \( OR \) 2.3 [1.1-4.5]
• Largest effect in 4 families: 20/219 rel vs 1/164 spouses p=0.0001 \( OR \) 16 [2.2-123]
• This study was before XP genes cloned thus no lab assay for confirmation XP genotype
CANCER RISK IN XP HETEROZYGOTE MICE

- *XPA* or *XPC* homozygous knockout mice have increased UV cancer susceptibility

- 1995 Sands et al: No increased post-UV skin cancer in *XPC* heterozygous mice after short exposure time

- 2000 Cheo et al: *XPC* heterozygous mice had increased post-UV skin cancer frequency after long exposure time (50 to 100 weeks)
PROPOSED STUDY TO EXAMINE CANCER RISK IN XP HETEROZYGOTES

Study of XP kindreds in US

1. Determine causative mutation in each kindred
2. Ascertain family members and determine cancer status
3. Determine presence or absence of causative mutation in DNA from family members using molecular diagnostic assays
4. Determine cancer frequency in XP heterozygotes and normal family members
## XERODERMA PIGMENTOSUM FAMILIES STUDIED AT THE NIH

<table>
<thead>
<tr>
<th>COMPLEMENTATION GROUP</th>
<th>NUMBER OF FAMILIES</th>
<th>NUMBER OF MUTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>G</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>VARIANT</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>56</td>
<td>44</td>
</tr>
</tbody>
</table>