Xeroderma pigmentosum
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Identity

Inheritance
Recessive autosomal; occurrence is favored by consanguinity; frequency is \( 0.3/10^5 \) with large geographical variations; higher frequency observed in Tunisia \( (10/10^5, \text{role of consanguinity}) \) and in Japan \( (1/10^5) \); rare in black people.

Clinics

Note
Xeroderma pigmentosum (XP) is caused by a defect in nucleotide excision repair mechanisms; various clinical aspects and intensity of signs are described according to the gene involved (7 known complementation groups) and type of mutation.

Phenotype and clinics
Severe sun photosensitivity (poikilodermia): induced precocious cutaneous lesions, concomitant to first sun exposures, on the exposed areas (hands, arms, face); dry skin, senile-like, cutaneous retractions (premature aging of the skin).
Photophobia, often the first sign, before cutaneous lesions; followed by bilateral cataract; increased risk of ocular benign and malignant tumors.
Neurological signs (14 to 40% of patients): mental retardation, pyramidal syndrome, peripheral neuropathia; more severe central nervous system (CNS) disorders are observed when mutations occur in XPA DNA binding site.
Clinical heterogeneity: related to genetic heterogeneity of the disease (7 known complementation groups A, B, C, D, E, F, G and 7 characterized genes). Intensity and precocity of signs are dependent on the gene involved; groups A, C, D and G are associated with a more severe disease.
The same genes are implicated in two related diseases: Cockayne syndrome (groups B, D and G) and trichothiodystrophy (groups B and D).

Neoplastic risk
Propensity to cutaneous tumors after sun exposure (risk X 1000 to develop cancer on sun -exposed areas of the skin): benign lesions, multiple basal cell carcinomas and spinal carcinomas (occurring in 2 to 40 year old patients, median age 8 yrs), malignant melanomas slightly later than carcinomas (risk x 2000 compared to normal population), rarely other skin tumors (fibrosarcomas, angiosarcomas).
Propensity to various solid tumors (mainly brain tumors, x 10 to 20 fold in comparison with general population).

Treatment
Photoprotection; genetic counseling; treatment of malignant tumors.

Evolution
Progressively increasing number of cutaneous, ocular and other solid tumors; cutaneous atrophy with numerous scars and aesthetic damage; skin abnormalities comparable to what is clinically and histologically observed with aging; blindness; severe mental retardation.

Prognosis
2/3 death before adult age.
Above: characteristic aspect of evolved lesions of the face in an XP patient. To be noted multiple scars of carcinomas and an aged aspect of the skin with poikilodermia. Below: multiple basocellular carcinomas on the face of an XP patient. Thick arrow points to a recent lesion, and thin arrow to a scar of an old lesion - Courtesy Daniel Wallach.

**Cytogenetics**

**Inborn conditions**

Hypermutability after UV irradiation in cell cultures; no increased of spontaneous chromosome abnormalities in lymphocytes of fibroblasts; however, after UV-exposure an increased number of sister chromatid exchanges (SCE) and chromosome aberrations are observed (mainly chromatid-type abnormalities); fibroblasts express an increased sensitivity to chemical mutagens; there is no cytogenetic feature useful for XP diagnosis.

**Genes involved and proteins**

*Note*

The clinical and cytologic XP heterogeneity is the consequence of the genetic heterogeneity: 7 complementation groups (XPA to G) plus an additional variant form, evidenced by somatic cell fusion experiments.

The genes involved are: XPA, located in 9q22, XPB, also called ERCC3 (ERCC for Excision-Repair Cross Complementing rodent repair deficiency), located in 2q21, XPC, located in 3p25, XPD, also called ERCC2, located in 19q13, XPE, located on chromosome 11 XPF, also called ERCC4, located in 19q13 XPG, also called ERCC5, located in 13q32, and XPV, also called Pol eta, and located in 6p12-21.

All XP genes are implicated in various steps of the NER (nucleotide excision repair) system, except the XP variant that is mutated in a mutagenic DNA polymerase (POL H) able to bypass the UV-induced DNA lesions; various alterations of the same gene may involve various phenotypes Cockayne syndrome, trichothiodystrophy).
References


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