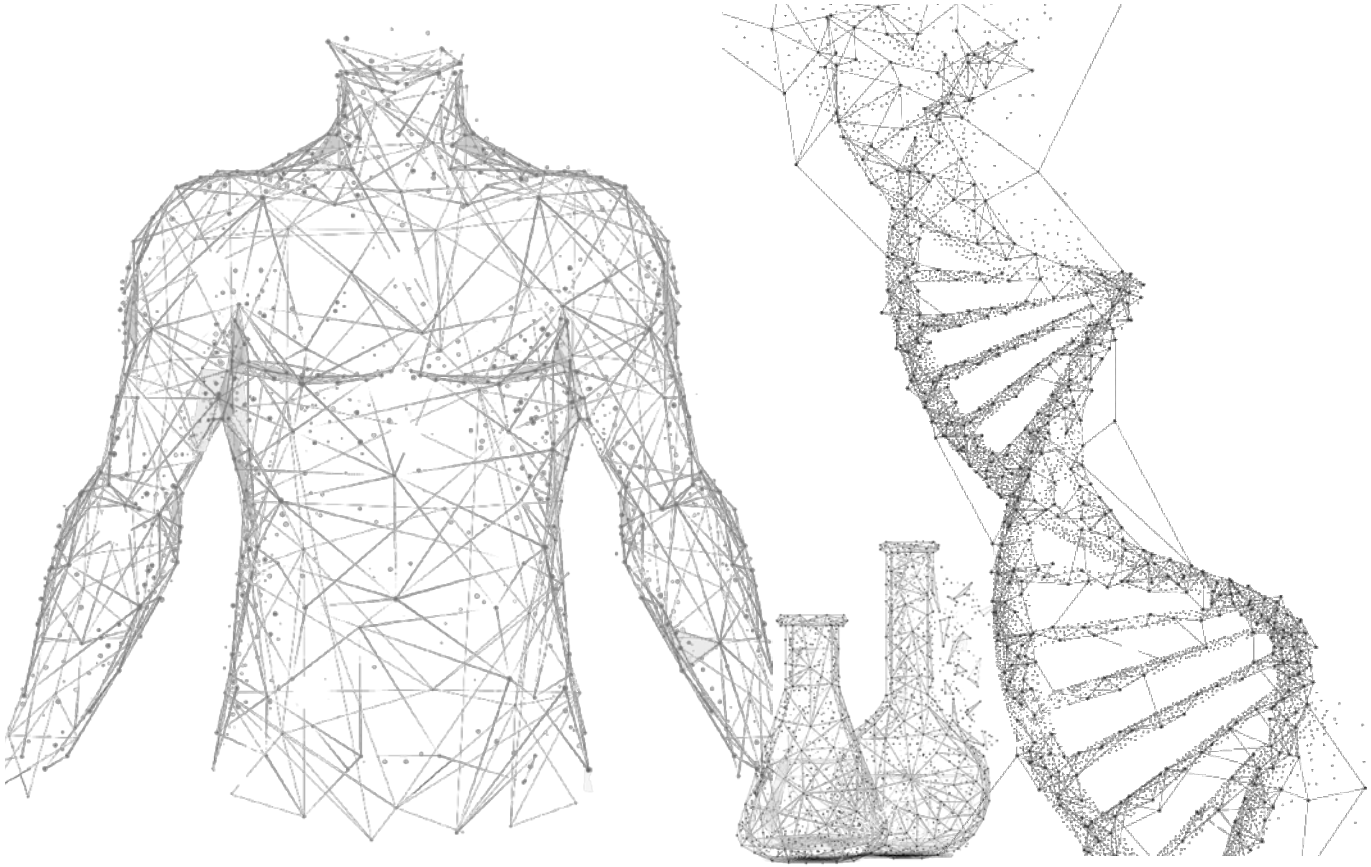


DNA Repair and DNA Repair Disorders

San Luis Potosi State University (UASLP) Mexico
Molecular Biology Course, Faculty of Medicine graduate program

Dr. Christian A. García-Sepúlveda

Viral & Human Genomics BSL-3 Laboratory

Last updated January 28, 2025 v3

Diseases caused by DNA repair machinery deffects

Also known as “DNA repair deficient disorders.”

Knockouts of genes involved in DNA repair are embryonic lethal.

Most DRDDs show varying degrees of accelerated aging or predisposition to cancer, sometimes both.

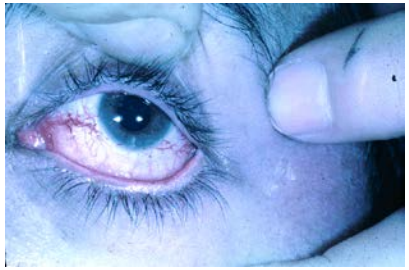
Defects in DNA repair are seen in almost all “accelerated aging diseases” in which tissues, organs or systems age prematurely.

Also known as segmental progerias.

- Ataxia telangiectasia
- Bloom syndrome
- Cockayne syndrome
- Fanconi anemia
- Progeria (Hutchinson-Gilford syndrome)
- Rothmund-Thomson syndrome
- Trichothiodystrophy
- Werner syndrome
- Xeroderma pigmentosum

Ataxia telangiectasia

Rare neurodegenerative syndrome characterized by motor disorders and dilation of small vessels.



1:40,000 to 1:100,000 live births.

ATM gene defect responsible for identifying double-strand breaks, recruiting translesional DNA reparases to the site, and preventing new replication cycles.

Affects the cerebellum, causing movement and coordination difficulties which progresses to oculomotor apraxia (difficulty moving eyes from side to side) and swallowing problems, distorted and slurred speech.

Causes immunocompromise that predisposes to infections (sinusitis, bronchitis, and pneumonia).

Increases risk of cancer.

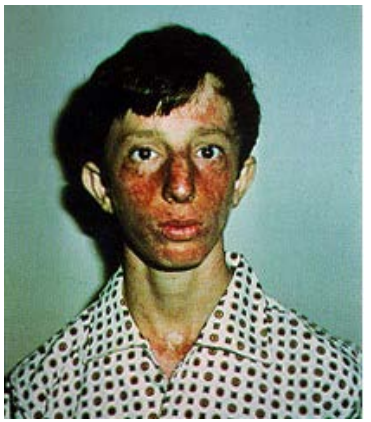
Symptoms evident in early childhood (4 to 5 years), worsening in late childhood.

Infants' flaccid posture when sitting (drunken posture).

Variable life expectancy (ca 25 years), death from COPD and cancer.

Bloom Syndrome

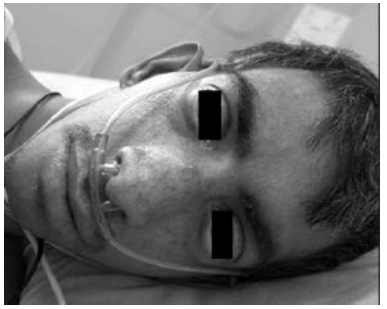
Also Bloom–Torre–Machacek syndrome (described in 1954).



Rare autosomal recessive disorder with high genomic instability and excessively high homologous recombination (see image below denoting sister chromatid exchanges).

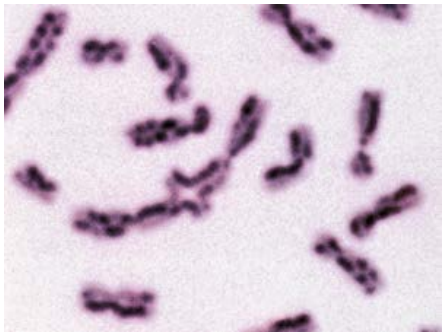
1:50,000 births.

Mutation in BLM gene, member of the RecQ helicase family involved in DNA denaturation during transcription, replication and repair.



Short stature, sloping shoulders, high-pitched voice, long thin face, micrognathia and prominent ears/nose.

Erythematous, telangiectatic, scaly butterfly-shaped skin rash on cheeks and nose.



Moderate immunodeficiencies particularly of certain classes of Igs (pneumonia, otitis and COPD).

Hypogonadism and infertility, affects men and women equally.

Death from COPD or cancer around age 25.

Cockayne Syndrome

Autosomal recessive mutations in the ERCC6 (CSB) or ERCC8 (CSA) genes.

Affects transcription-coupled nucleotide excision repair (TC-NER), leading to sensitivity to uv radiation.

Progressive neurodegeneration, developmental delays, intellectual disability, and motor impairment.

Dwarfism, microcephaly, and poor weight gain.

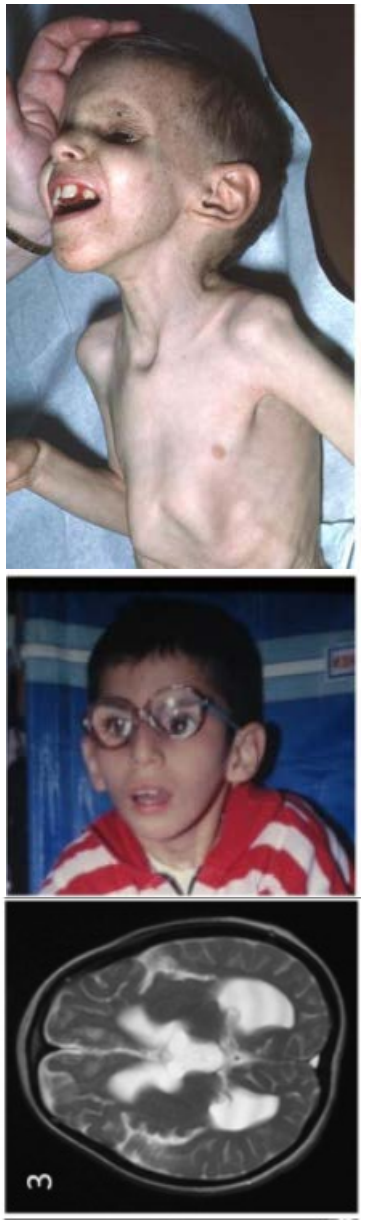
Extreme sensitivity to sunlight, leading to early skin aging.

Sunken eyes, thin nose, large ears, and aged appearance.

Progressive sensorineural hearing loss and cataracts are common.

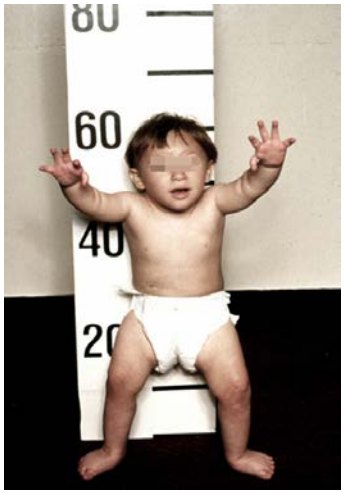
Resembles a progeroid syndrome, with early-onset degenerative changes.

Life expectancy varies; severe cases (type I & II) often lead to death in childhood or early adolescence.



Fanconi's anemia

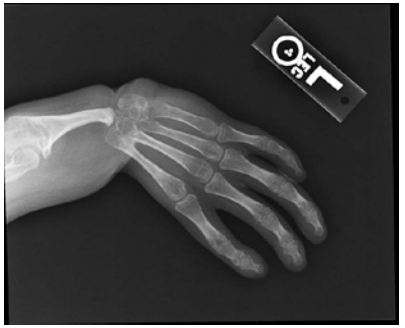
Rare, autosomal recessive (or x-linked FANCB) disorder characterized by chromosomal instability, bone marrow failure, congenital abnormalities, and predisposition to cancer.



Global incidence of 1 in 130,000 to 1 in 300,000 live births, but more common in ashkenazi jews, afrikaners, and spanish gypsies.

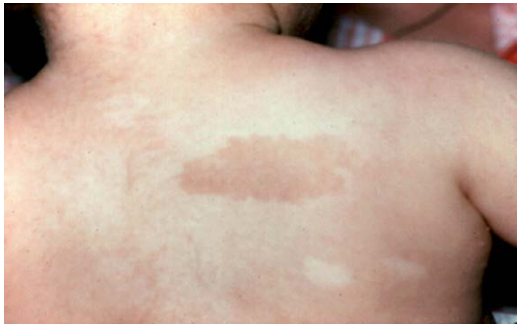
Mutations in one of 23 known FA genes, most commonly FANCA, FANCC, or FANCG crucial for repairing dna crosslinks and genomic stability.

Progressive bone marrow failure with pancytopenia (anemia, neutropenia, and thrombocytopenia) and increased susceptibility to infections, fatigue, and bleeding.



Short stature, radial ray defects (absent or hypoplastic thumbs), absent radii.

Café-au-lait spots and generalized hyperpigmentation.



Horseshoe kidneys, absent kidneys, or structural abnormalities.

Microcephaly, small eyes, or other craniofacial abnormalities.Hearing loss.

Hutchinson-Gilford Syndrome (progeria)

Rare, fatal, autosomal dominant genetic disorder characterized by features of accelerated aging in children.

Extremely rare, estimated incidence of 1 in 20 million live births worldwide (100–150 cases are known globally at any given time).

De novo mutations in lmna gene, which encodes lamin a, a protein critical for nuclear structure and function.

Symptoms typically begin between 6 to 18 months of age

Profound failure to thrive despite normal birth weight.

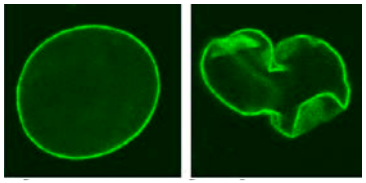
Short stature, low weight, disproportionately large head, micrognathia, thin, beaked nose.

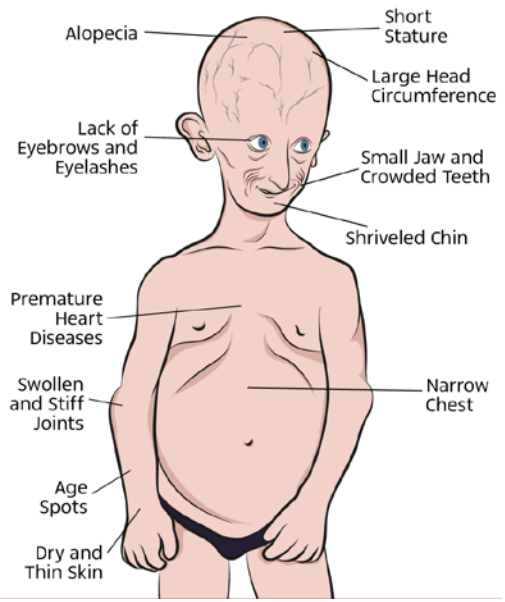
Thin, tight, and wrinkled skin resembling scleroderma, loss of subcutaneous fat, alopecia (including scalp, eyebrows, and eyelashes).

Delayed or abnormal dentition, progressive arteriosclerosis.

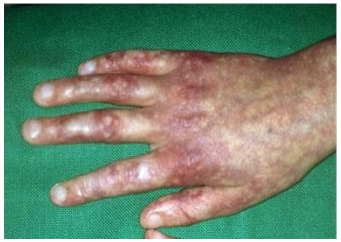
Unlike other aging syndromes, there is no cognitive impairment; intellectual development remains normal.

2 year old boy



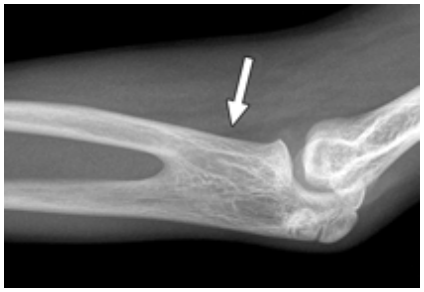


Rothmund-Thomson Syndrome



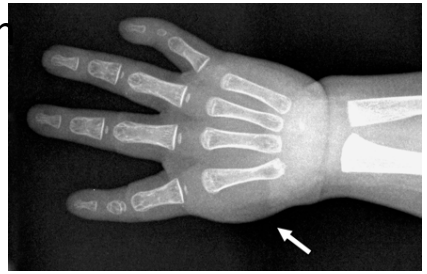
Rare autosomal recessive genodermatosis characterized by dermatologic, skeletal, and systemic abnormalities, with a predisposition to osteosarcoma.

Extremely rare, 1:1,000,000 to 1:2,000,000 births worldwide.



Mutations in the RECQL4 gene, which encodes a helicase enzyme involved in DNA repair and genome stability.

Manifests in infancy or early childhood, changes appearing by age 1.



Poikiloderma: Hyperpigmentation, hypopigmentation, telangiectasias, and skin atrophy in sun-exposed areas, photosensitivity is common.

Hypoplastic or absent thumbs, Radial ray defects, Short stature, Delayed bone development or osteoporosis.

Sparse scalp hair, eyebrows, and eyelashes, along with brittle or dystrophic nails.

Cataracts, at risk for skin cancers (e.g., basal cell carcinoma) and hematologic malignancies.

Infertility or subfertility due to gonadal dysgenesis.

Trichothiodystrophy Syndrome (IBIDS)

Autosomal recessive mutations in ercc2 (xpd), ercc3 (xpb), or gtf2h5 genes.

Affects transcription-coupled nucleotide excision repair (tc-ner).

Ibids: ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature.

Brittle, sulfur-deficient hair "tiger-tail" banding under polarized light.

Ichthyosis: scaly, dry skin resembling ichthyosis vulgaris.

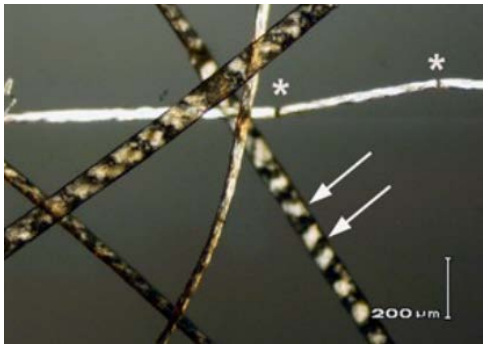
Intellectual disability, developmental delay, and motor deficits.

Uv light sensitivity, similar to xeroderma pigmentosum.

Growth retardation and failure to thrive are common.

Immunodeficiency and increased susceptibility to infections.

No increased cancer risk unlike other dna repair disorders.



Werner's Syndrome

Also known as adult progeria, a very rare autosomal recessive disease characterized by premature aging described in 1904.

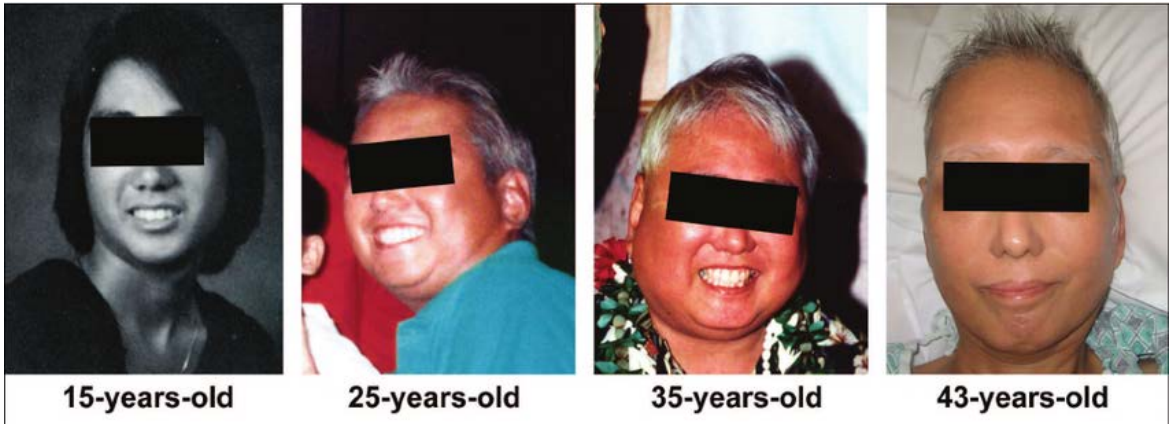
Associated with mutations in the WRN gene (chromosome 8) also known as RecQL2, which encodes a 3'-5' helicase.

Symptoms seen after 10 years of age, accelerating after puberty and extreme by age 40.

Absence of pubertal growth spurt, thinning and discoloration of hair, voice changes, thickening of skin, diabetes mellitus, cataracts, hypogonadism, cancer and atherosclerosis.

Characterized by accelerated telomere shortening and genomic instability.

Death usually from myocardial infarctions or cancer by age 50.



Xeroderma pigmentosum

Autosomal recessive disorder with defects in actinic damage repair (especially UV).

Affects 1:250,000 live births, both sexes, all races (most common in Japanese).

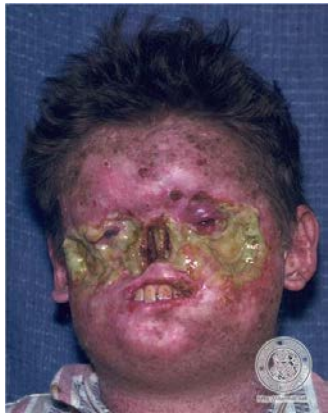
Nucleotide excision repair (NER) mechanisms are affected leading to accumulation of UV damage (thymidine dimers) and activation of proto-oncogenes.

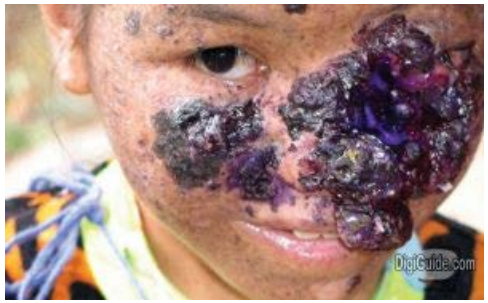
Extreme photosensitivity (“Children of the dark”), ephelides, solar keratosis, photoconjunctivitis, telangiectasias and corneal ulcers.

Appearance of basal cell carcinomas, melanomas and squamous cell carcinomas.

Severe facial deformity in response to injury.

8 types or variants of XP described to date, less than 40% survive to 20 years of age.





Laboratorio de Genómica Viral y Humana

Instalaciones de Alta Contención Biológica Nivel de Bioseguridad 3 (BSL-3) CDC-certificadas

Facultad de Medicina UASLP
San Luis Potosí, México

www.genomica.uaslp.mx

GenomicaUASLP

YouTube GenomicaUASLP

Content copyright and license

The Viral and Human Genomics Laboratory is committed to promoting the human rights of free access to knowledge and to receiving the benefits of scientific progress and its applications by providing universal access to all the resources and publications it produces. This is in agreement with article 15 of the United Nations International Covenant on Economic, Social and Cultural Rights published on April 30, 2020.

(Last updated: August 23, © 2024.)