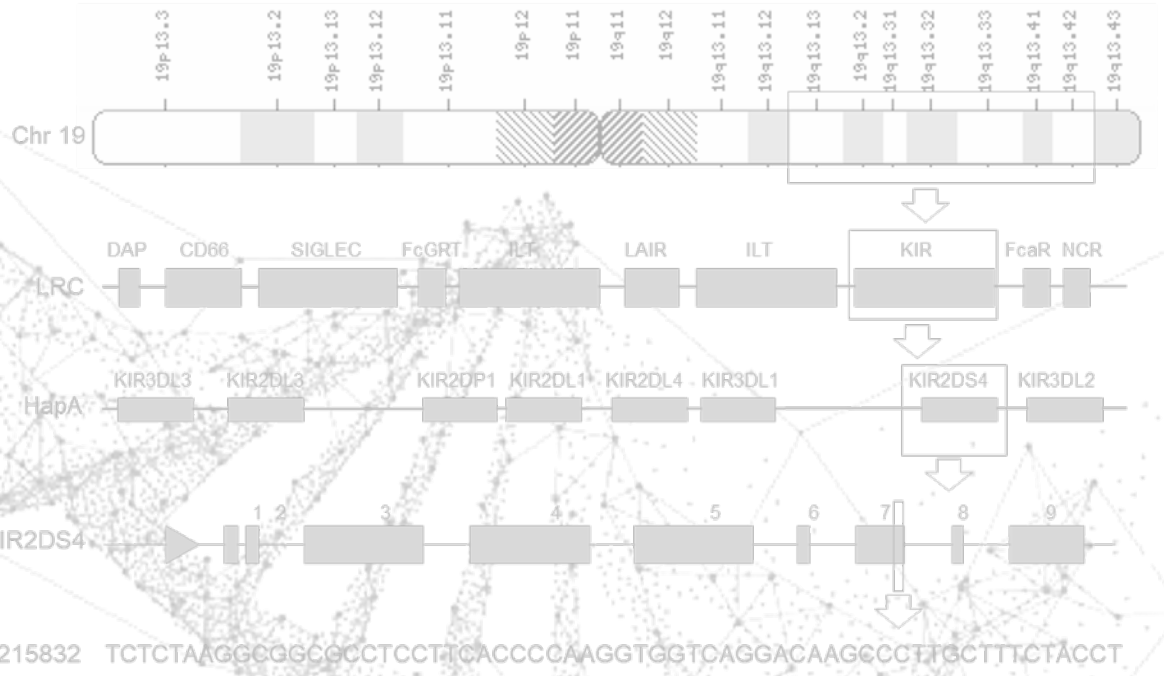

Mutagenesis, DNA repair and repair defect diseases

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

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Viral & Human Genomics BSL-3 Laboratory

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Mutations and polymorphisms

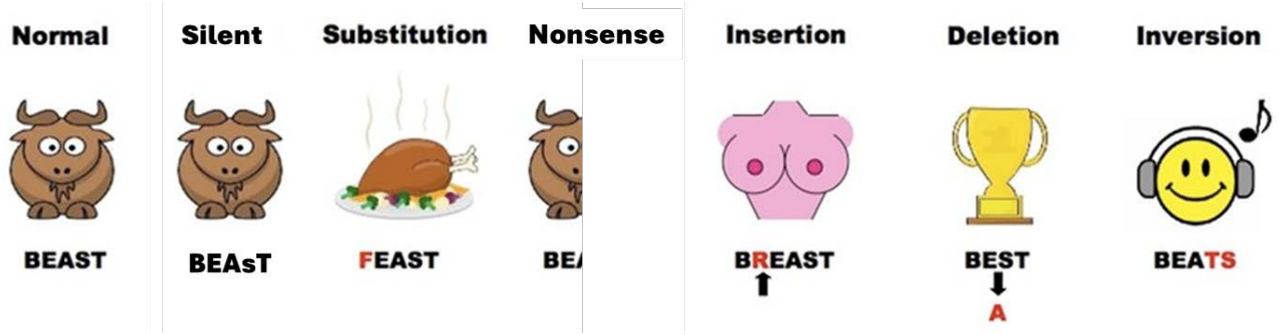
Mutations are fundamental to genetics and evolution.

Influencing everything from biological variation, speciation, disease mechanisms, and evolutionary processes.

A mutation is a permanent alteration in the DNA sequence of an organism.

Affect a single nucleotide or a large chromosomal segment.

Arise spontaneously due to errors in DNA replication or are induced by environmental factors (radiation, chemicals, and viruses).



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Importance of mutations

Without mutations, evolution by natural selection would not be possible.

Source of Genetic Variation

- Mutations introduce new alleles, increasing genetic diversity within a population.
- This diversity allows species to survive environmental changes, predation, or disease.

Driving Force of Evolution

- Mutations contribute to natural selection creating traits that offer survival advantages.

Neutral, Beneficial, and Harmful Mutations

- Most mutations are neutral (do not affect survival).
- Some are beneficial, leading to advantages (sickle cell trait resistance to malaria).
- Others are harmful, causing genetic disorders like cystic fibrosis or muscular dystrophy.

Mutations and Genetic Disorders

- Monogenic disorders caused by a single mutation (Sickle cell anemia).
- Polygenic disorders involve multiple genes and environmental factors (Diabetes).
- Cancer caused by mutations in genes regulating cell division, lead to uncontrolled growth.

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Error rate of polymerases

RNA viruses have high mutation rates (Flu & SARS-CoV-2) as their RNA-dependent RNA polymerases (RdRp) lack proofreading activity.

Retroviral reverse transcriptase (RT) is error-prone and leads to quasispecies.

DNA virus polymerases have proofreading functions and lower mutation rates.

Bacteria have high-fidelity polymerases (DNA pol III), with 3' → 5' exonuclease error correction.

In vitro bacterial DNA polymerases (DNA pol I) used for PCR have 1/1000 error rate.

Eukaryotic polymerases have high fidelity and proofreading abilities and mismatch repair (MMR) system further reduces error rate and makes replication highly accurate.

In cancer cells, defects in DNA repair increase the mutation rate, leading to genomic instability.

Organism	Polymerase	Error Rate
RNA Viruses	RNA polymerase (RdRp)	~10^{-3} – 10^{-5}
Retroviruses	Reverse Transcriptase	~10^{-4} – 10^{-6}
DNA Viruses	DNA polymerase (with proofreading)	~10^{-6} – 10^{-8}
Bacteria	DNA polymerase III (proofreading)	~10^{-7} – 10^{-8}
PCR Taq	DNA polymerase without proofreading	~$10^{-}3$
Eukaryotes	DNA polymerase δ and ε (proofreading + MMR)	~10^{-8} – 10^{-9}

Mutations per nucleotide per replication cycle.

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Mutation types

Point Mutations

- Transitions and transversions
- Silent
- Missense
- Nonsense Mutations

Frameshift Mutations

- Insertions and Deletions (Indels)
- Effects on Protein Translation

Large-Scale Mutations

- Numeric chromosomal anomalies
- Structural chromosomal anomalies
  - Deletions
  - Duplications
  - Inversions
  - Translocations
- Copy Number Variations (CNVs)

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Transitions and transversions

Transition mutations (R to R or Y to Y)

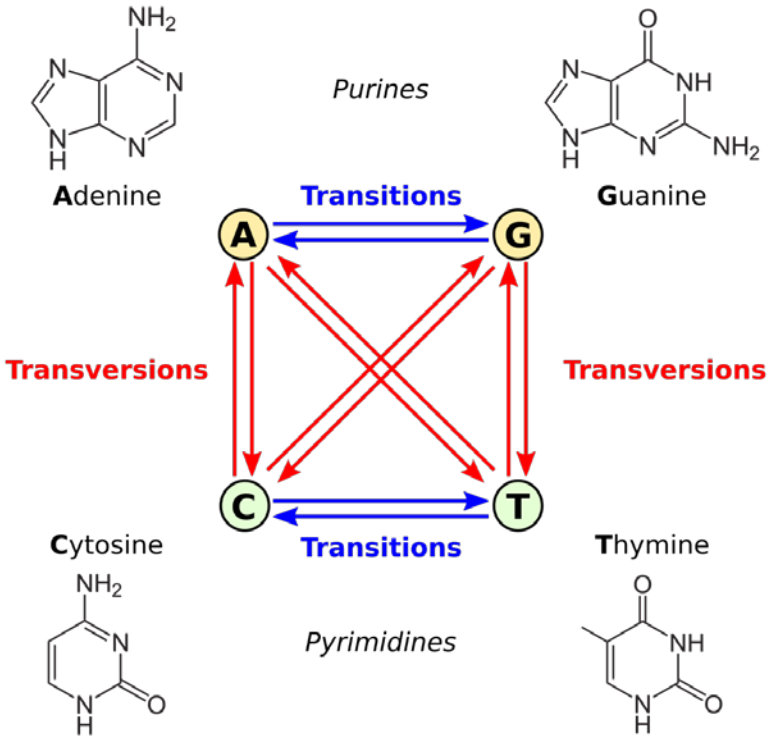
- More common (structural similarity of bases).
- Less disruptive to DNA double helix
- Better tolerated by repair mechanisms.

Transversion mutations (R to Y or Y to R)

- Less frequent due to the structural differences
- Make mispairing less likely.

Transitions more frequent than transversions, typically 2:1 to 4:1.

In mammals, transitions at CpGs occur at a rate **10 – 50 times higher** than other substitutions due to the **methylation and spontaneous deamination** of 5-methylcytosine.



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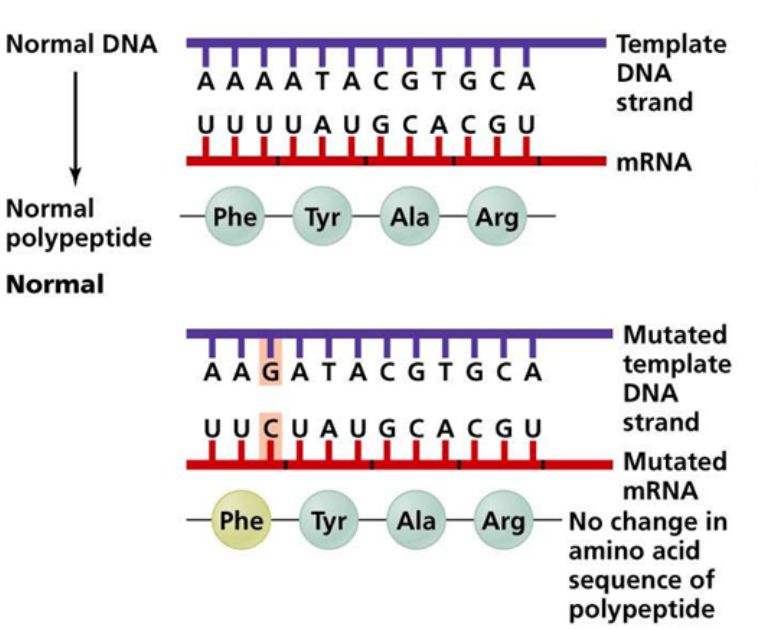
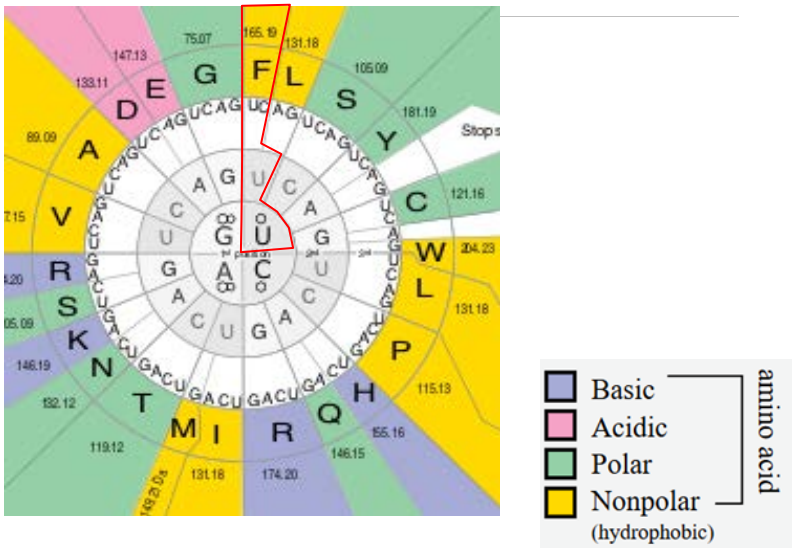
Silent mutations (synonymous substitution)

A nucleotide change does not alter the amino acid sequence due to redundancy in the genetic code.

GAA → GAG (Both code for Glutamate)





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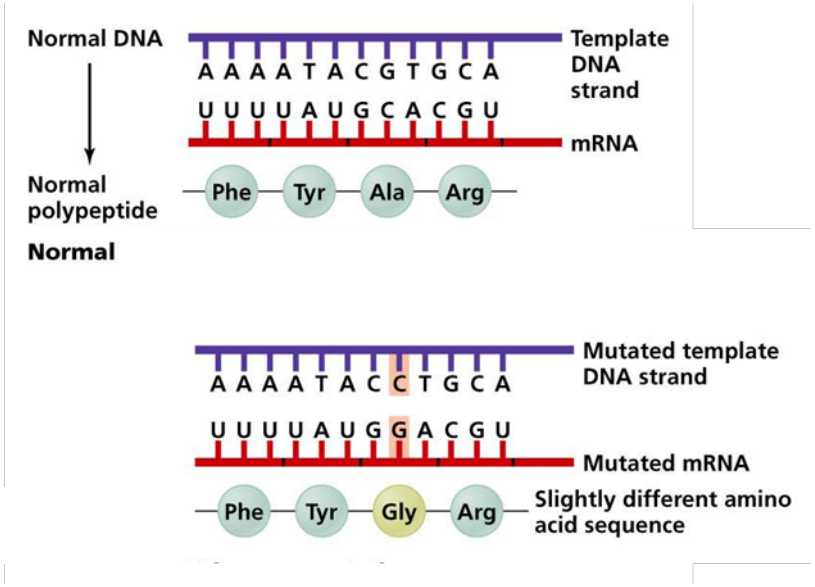
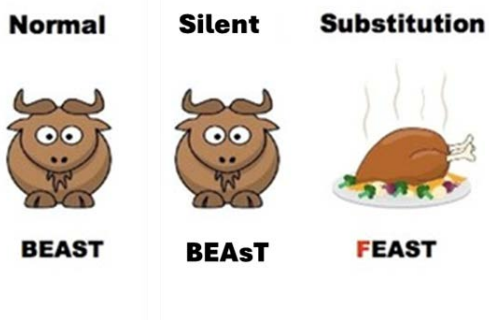
Missense mutations (Non-synonymous substitution)

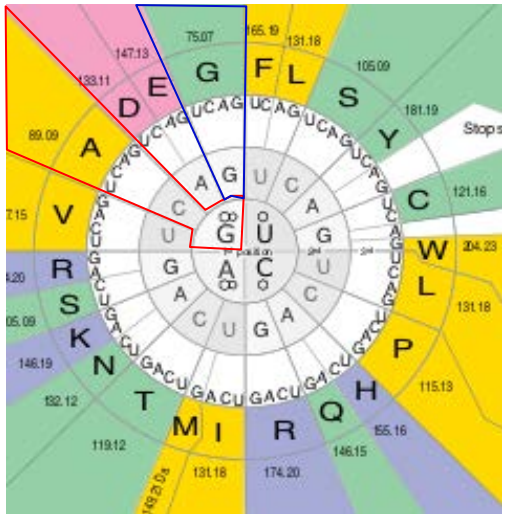
A nucleotide change results in a different amino acid, potentially altering protein function.

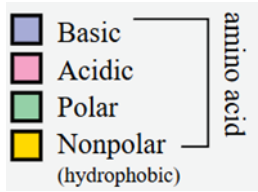
GCA → GGA (Alanine → Glutamate)

Missense mutations can be **conservative** (similar properties between amino acids) or **non-conservative** (drastically different properties).









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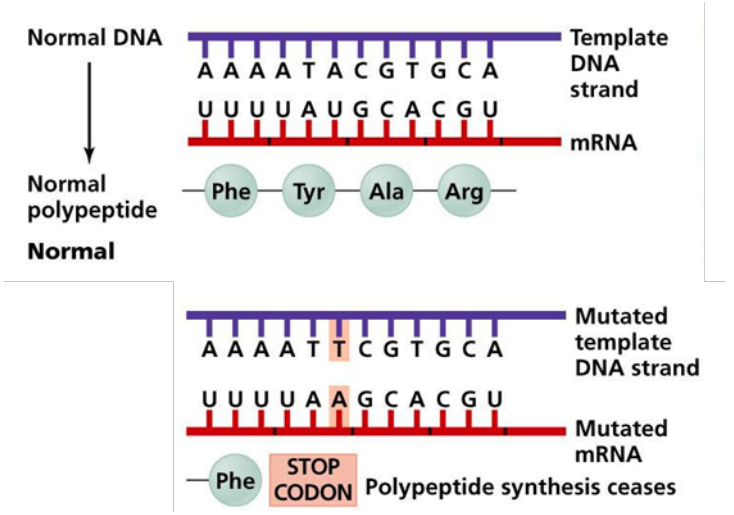
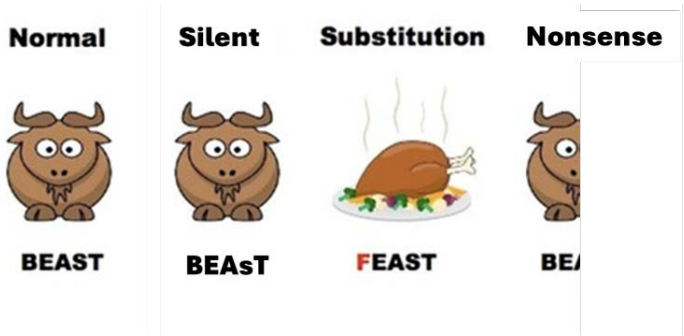
Nonsense mutations (Premature stop codon)

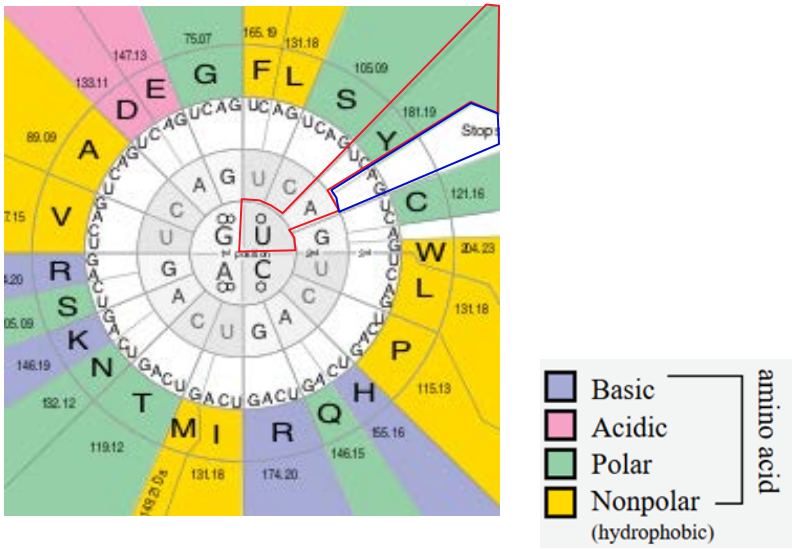
A nucleotide change converts a codon into a stop codon, leading to premature termination of translation.

UAU → UAA (Tyrosine → Stop codon)

Nonsense mutations often produce nonfunctional or truncated proteins, which can lead to severe diseases (e.g., Duchenne muscular dystrophy).







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Frameshift insertions or deletions (Indels)

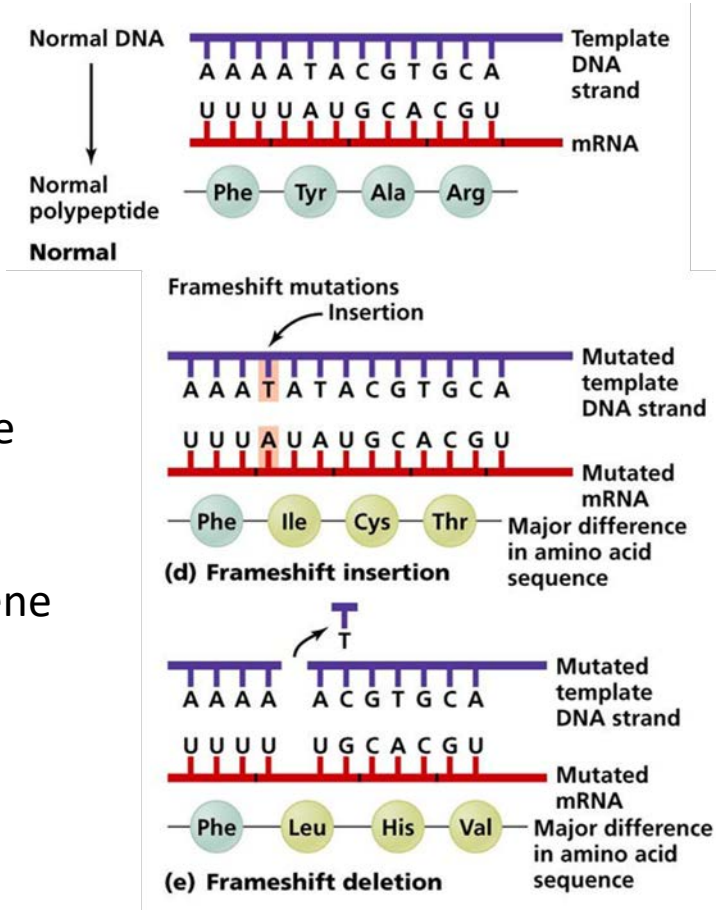
Insertion: Addition of one or more nucleotides.
Deletion: Removal of one or more nucleotides.

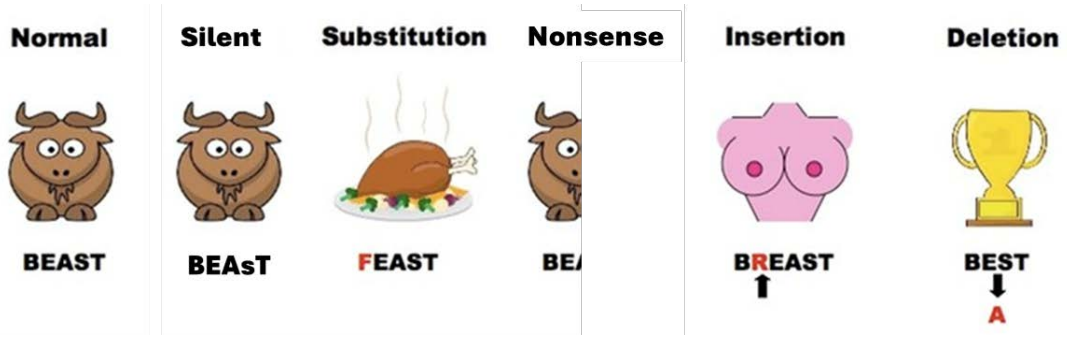
Alters all downstream codons, leads to a completely different amino acid sequence.

Often results in a nonfunctional protein due to premature stop codons.

Cystic fibrosis caused by 3 bp deletion (ΔF508) in CFTR gene dropping a Phe.

Tay-Sachs disease caused by 4 bp insertion in HEXA gene, Nonfunctional enzyme & lipid accumulation in neurons.





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Large scale mutations

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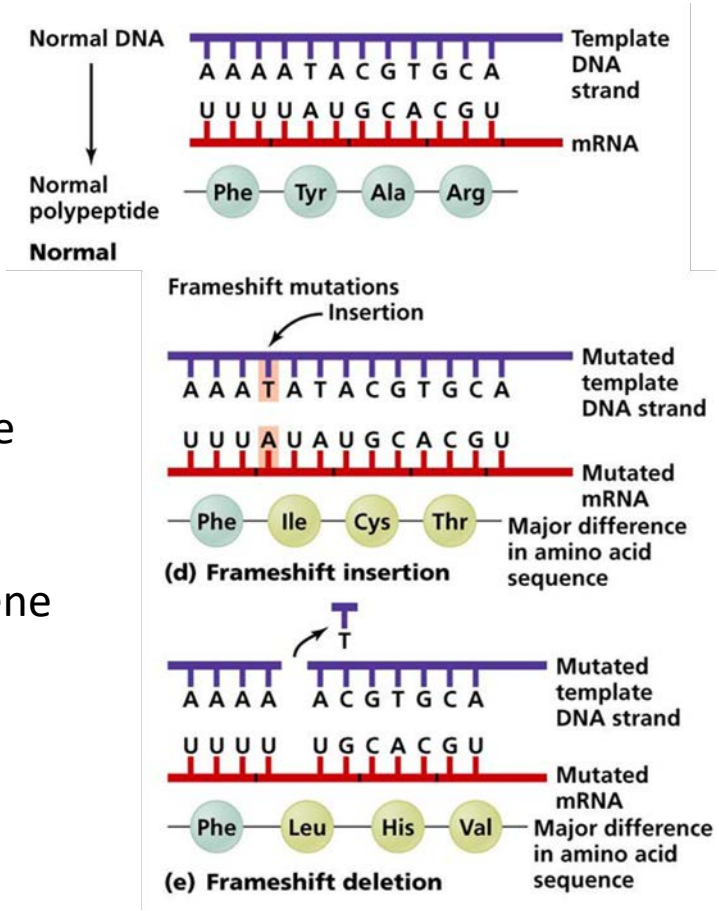

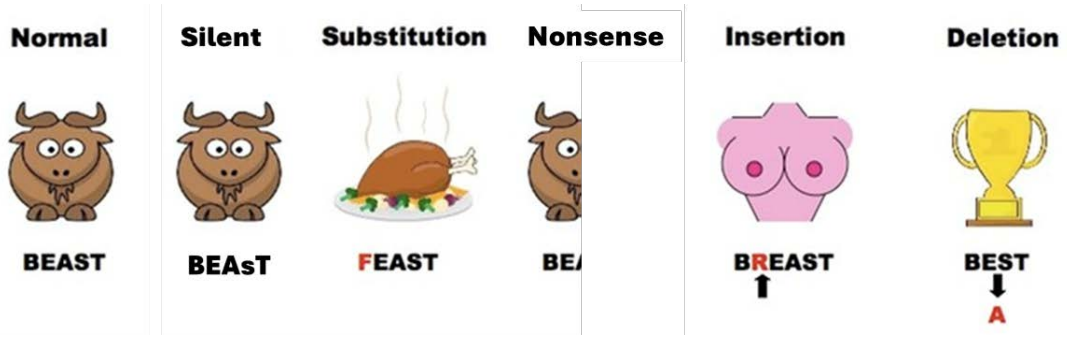

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Numeric anomalies (aneuploidy)

Condition in which a cell has an abnormal number of chromosomes, deviating from 2n count.

Commonly due to meiotic nondisjunction, where homologous chromosomes (Meiosis I) or sister chromatids (Meiosis II) fail to separate properly.

Mitotic nondisjunction can also occur post-zygotically, leading to mosaicism.

Risk of aneuploidy increases with advanced maternal age….

42.9% of embryos are aneuploid.	
Maternal age	**% normal embryos**
< 25 years	70%
25–29 years	48%
30–34 years	42%
35–39 years	34%
> 39 years	11%

Autosomal trisomies due to maternal meiosis I errors (~70-90% of cases).

Most trisomies (90%) are lethal in utero.

Alll autosomal monosomies are lethal.

- Monosomy (2n−1)
- Trisomy (2n+1)
- Tetrasomy (2n+2)
- Pentasomy (2n+3)

X inactivation compensation in Turner syndrome (45,X), Klinefelter (47,XXY), and XYY syndrome (47,XYY).

Sex chromosome aneuploidies common but often undiagnosed due to mild phenotypes.

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Structural anomalies

Deletions, Duplications, Inversions and Translocations.

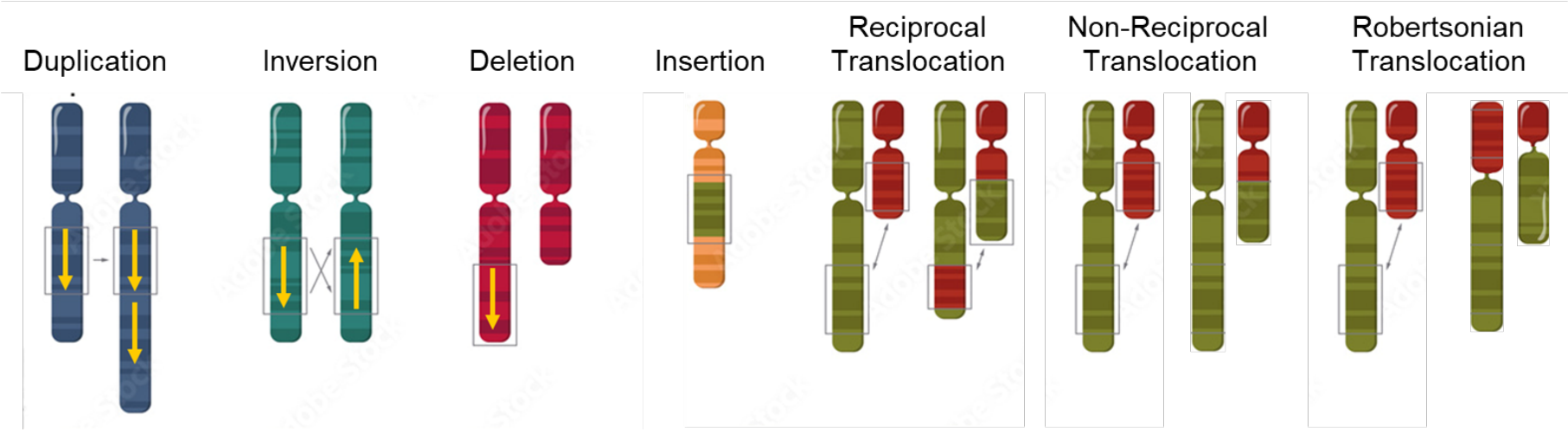
Involve rearrangements or alterations in chromosome structure due to double-strand DNA breaks.

Reciprocal translocations exchange between two chromosomes like t(9;22) in chronic myeloid leukemia.

Robertsonian translocations due to acrocentric fusion at centromere t(14;21) familial Down syndrome.

Errors in nonhomologous end-joining (NHEJ) or homologous recombination (HR) or Non-allelic homologous recombination (NAHR).

Balanced rearrangements (inversions, reciprocal translocations) may be asymptomatic.



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Copy Number Variations (CNVs)

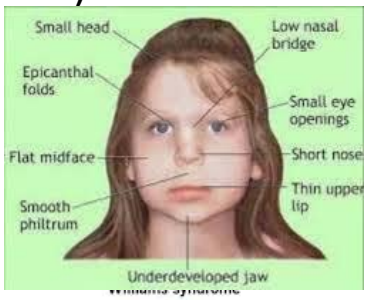
Genomic alterations involving deletions or duplications of DNA segments ≥1 kb in size.

Account for 4–12% of the human genome & contribute more variation than SNPs.

Regions with duplications lead to non-allelic homologous recombination (NAHR).

Affecting gene dosage.

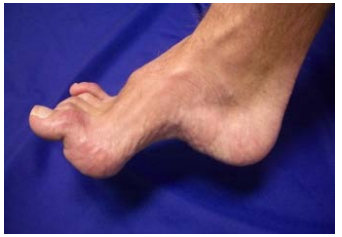
Some CNVs are benign others are associated with disease susceptibility.



DiGeorge syndrome (22q11.2 deletion)
Congenital heart defects, immunodeficiency, and developmental delay.

Williams syndrome (7q11.23 deletion)
Distinctive facial features, cardiovascular anomalies, hypersocial behavior.

Charcot-Marie-Tooth disease type 1A (17p12 duplication)
Peripheral neuropathy due to PMP22 overexpression.



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DNA Polymerases in prokaryotes

Five well-known enzymes.

DNA Pol I

DNA repair.

5’ - 3' exonuclease (Nick-translation)

3’ - 5' exonuclease (proofreading).

DNA Pol II

TLS (trans-lesional synthesis).

5’ - 3' polymerase.

3’ - 5' exonuclease.

DNA Pol III

Main prokaryotic replicase.

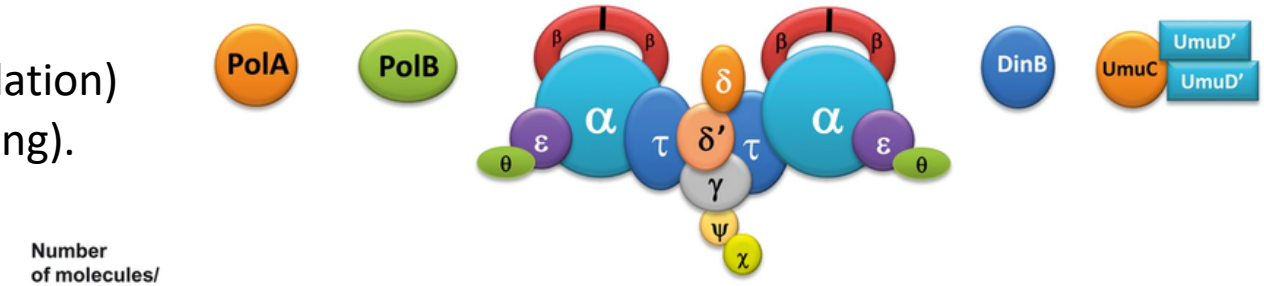
5’ - 3' polymerase.

3’ - 5' exonuclease.

DNA Pol IV and V

Members of family Y (Translesional Synthesis Polymerases).

	Pol I	Pol II	Pol III	Pol IV	Pol V
DNA polymerase family	A	B	C	Y	Y
Activity	5’-3’ polymerase 3’-5’ exonuclease 5’-3’ exonuclease	5’-3’ polymerase 3’-5’ exonuclease	5’-3’ polymerase 3’-5’ exonuclease	5’-3’ polymerase	5’-3’ polymerase
Number of molecules/ cell					
– SOS	400	50 - 75	10 - 20	150 - 250	< 15
+ SOS	400	350 - 1000	10 - 20	1200 - 2500	200
Biological functions in the cell	DNA replication, Okazaki fragment maturation, DNA repair	DNA replication (backup DNA polymerase), DNA repair, TLS	DNA replication DNA repair	TLS	TLS



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DNA Polymerases in eukaryotes

Polymerase[a]	Family	Catalytic subunit				Associated activities	Proposed functions
		Molecular mass (kDa)[b]	Human gene (alias)	Chromosomal location[c]	Yeast gene[d] (alias)		
α (alpha)	B	165	*POLA*	Xp22.1-p 21.3	*POL1 (CDC17)*	Primase	chromosomal replication, S-phase checkpoint, DSB repair
β (beta)	X	39	*POLB*	8p11.2	-	dRP & AP lyase	BER, single strand break repair
γ (gamma)	A	140	*POLG*	15q25	*MIP1*	3'→5' exonuclease, dRP lyase	mitochondrial replication, mitochondrial BER
δ (delta)	B	125	*POLD1*	19q13.3	*POL3 (CDC2)*	3'→5' exonuclease	chromosomal replication, NER, BER, MMR, DSB repair
ε (epsilon)	B	255	*POLE*	12q24.3	*POL2*	3'→5' exonuclease	chromosomal replication, NER, BER, MMR, DSB repair, S-phase checkpoint
ζ (zeta)	B	353	*POLZ (REV3)*	6q21	*REV3*		TLS, DSB repair, ICL repair?, SHM
η (eta)	Y	78	*POLH (RAD30, RAD30A, XPV)*	6p21.1	*RAD30*		TLS, SHM
θ (theta)	A	198	*POLQ*	3q13.33	-		ICL repair?
ι (iota)	Y	80	*POLI (RAD30B)*	18q21.1	-	dRP lyase	TLS?, BER?, SHM
κ (kappa)	Y	76	*POLK (DINB1)*	5q13	-		TLS
λ (lambda)	X	66	*POLL*	10q23	*POL4 (POLX)*	dRP lyase	DSB repair, BER?
μ (mu)	X	55	*POLM*	7p13	-	TdT	DSB repair
σ (sigma)	X	60	*POLS (TRF4-1)*	5p15	*TRF4*		sister chromatid cohesion
REV1	Y	138	*REV1*	2q11.1-q11.2	*REV1*	TdT (for dC)	TLS

Shcherbakova PV, et al. Functions of Eukaryotic DNA Polymerases. Sci Aging Knowledge Environ. 2003.

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μ (mu)	X	55	*POLM*	7p13	-	TdT	DSB repair
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REV1	Y	138	*REV1*	2q11.1-q11.2	*REV1*	TdT (for dC)	TLS

PRIMASE

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λ (lambda)	X	66	*POLL*	10q23	*POL4 (POLX)*	dRP lyase	DSB repair, BER?
μ (mu)	X	55	*POLM*	7p13	-	TdT	DSB repair
σ (sigma)	X	60	*POLS (TRF4-1)*	5p15	*TRF4*		sister chromatid cohesion
REV1	Y	138	*REV1*	2q11.1-q11.2	*REV1*	TdT (for dC)	TLS

REPAIRASES

Shcherbakova PV, et al. Functions of Eukaryotic DNA Polymerases. Sci Aging Knowledge Environ. 2003.

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DNA Polymerases in eukaryotes

Polymerase[a]	Family	Catalytic subunit				Associated activities	Proposed functions
		Molecular mass (kDa)[b]	Human gene (alias)	Chromosomal location[c]	Yeast gene[d] (alias)		
α (alpha)	B	165	*POLA*	Xp22.1-p 21.3	*POL1 (CDC17)*	Primase	chromosomal replication, S-phase checkpoint, DSB repair
β (beta)	X	39	*POLB*	8p11.2	-	dRP & AP lyase	BER, single strand break repair
γ (gamma)	A	140	*POLG*	15q25	*MIP1*	3'→5' exonuclease, dRP lyase	mitochondrial replication, mitochondrial BER
δ (delta)	B	125	*POLD1*	19q13.3	*POL3 (CDC2)*	3'→5' exonuclease	chromosomal replication, NER, BER, MMR, DSB repair
ε (epsilon)	B	255	*POLE*	12q24.3	*POL2*	3'→5' exonuclease	chromosomal replication, NER, BER, MMR, DSB repair, S-phase checkpoint
ζ (zeta)	B	353	*POLZ (REV3)*	6q21	*REV3*		TLS, DSB repair, ICL repair?, SHM
η (eta)	Y	78	*POLH (RAD30, RAD30A, XPV)*	6p21.1	*RAD30*		TLS, SHM
θ (theta)	A	198	*POLQ*	3q13.33	-		ICL repair?
ι (iota)	Y	80	*POLI (RAD30B)*	18q21.1	-	dRP lyase	TLS?, BER?, SHM
κ (kappa)	Y	76	*POLK (DINB1)*	5q13	-		TLS
λ (lambda)	X	66	*POLL*	10q23	*POL4 (POLX)*	dRP lyase	DSB repair, BER?
μ (mu)	X	55	*POLM*	7p13	-	TdT	DSB repair
σ (sigma)	X	60	*POLS (TRF4-1)*	5p15	*TRF4*		sister chromatid cohesion
REV1	Y	138	*REV1*	2q11.1-q11.2	*REV1*	TdT (for dC)	TLS

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DNA polymerase proofreading

The introduction of an incorrect nucleotide (or a nucleotide that does not pair correctly) leads the enzyme to move back one base and remove the nucleotide in the 3' ⍰ 5' direction.

Subsequently, the enzyme continues to advance.

The exonuclease activity may reside in the same subunit involved in DNA synthesis or in a different one.

The different known DNA polymerases have different degrees of fidelity (which depends on their proofreading capacity).

In general, the “proofreading” capacity increases the fidelity of the enzymes from 100,000 to 10,000,000

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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

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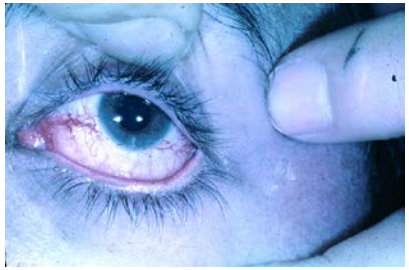
Ataxia telangiectasia

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.

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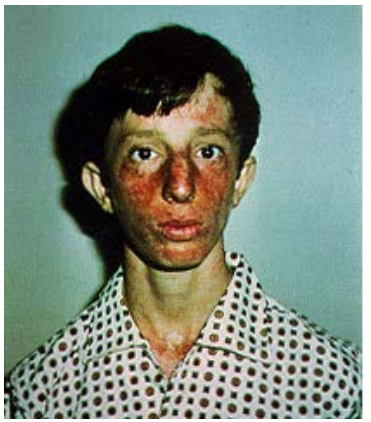
Bloom Syndrome

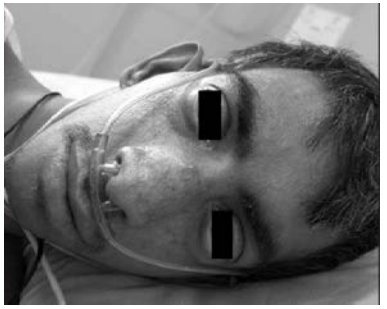
Also Bloom–Torre–Machacek syndrome (described in 1954).



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

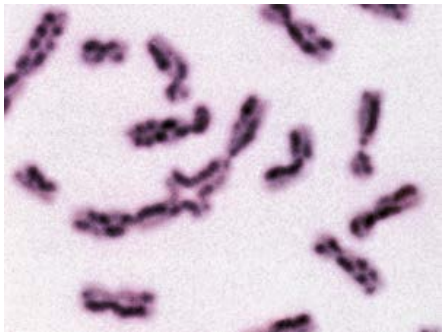
1:50,000 births.

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.

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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.

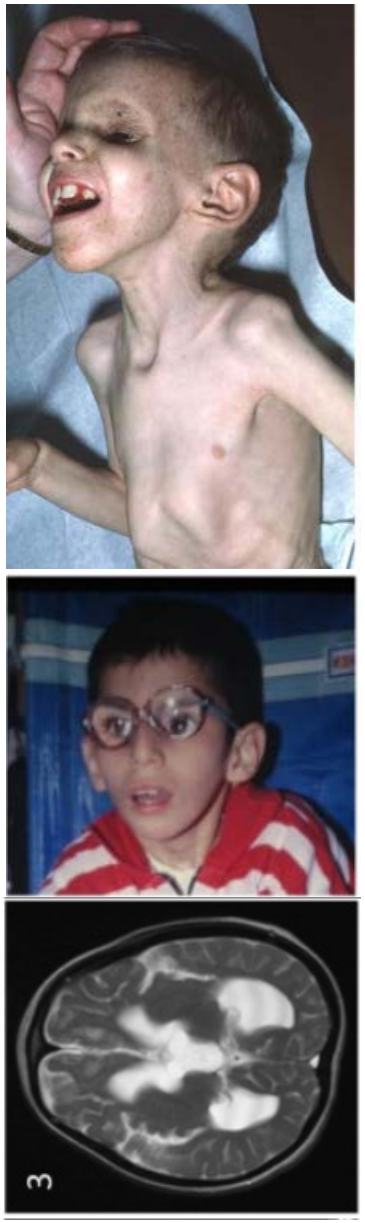
Extreme sensitivity to sunlight, leading to early skin aging.

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.



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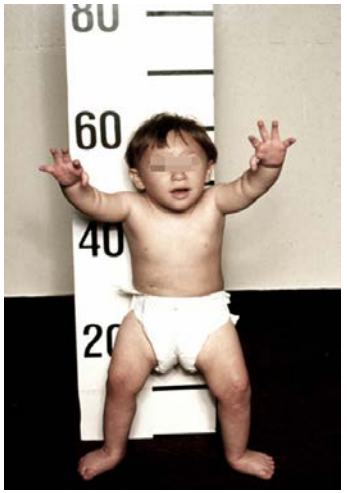
Fanconi's anemia

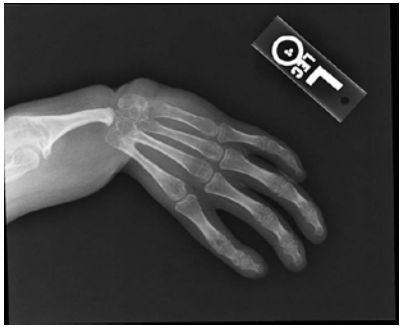
Rare, autosomal recessive (or x-linked FANCB) disorder characterized by chromosomal instability, bone marrow failure, congenital abnormalities, and predisposition to cancer.



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

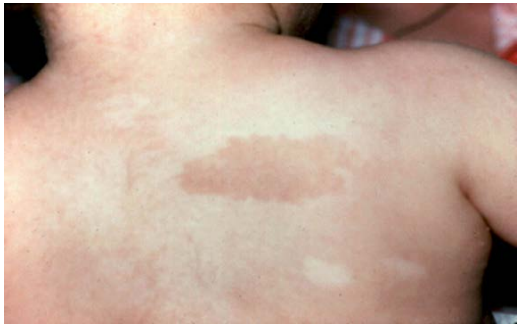
Mutations in one of 23 known FA genes, most commonly FANCA, FANCC, or FANCG crucial for repairing dna crosslinks and genomic stability.

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.

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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.

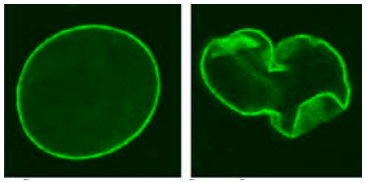
Short stature, low weight, disproportionately large head, micrognathia, thin, beaked nose.

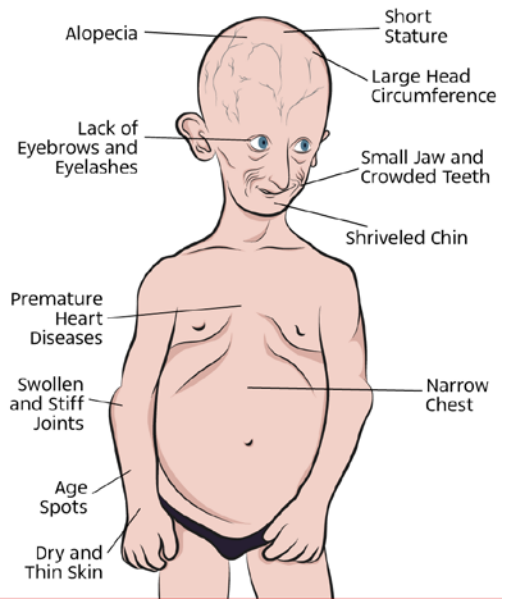
Thin, tight, and wrinkled skin resembling scleroderma, loss of subcutaneous fat, alopecia (including scalp, eyebrows, and eyelashes).

Delayed or abnormal dentition, progressive arteriosclerosis.

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

2 year old boy





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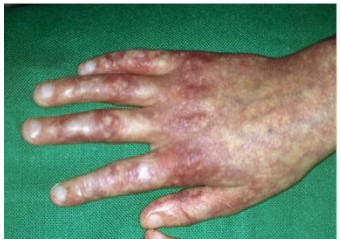
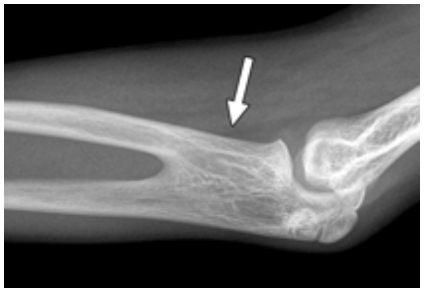
Rothmund-Thomson Syndrome



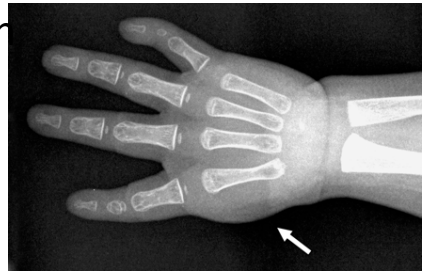
Rare autosomal recessive genodermatosis characterized by dermatologic, skeletal, and systemic abnormalities, with a predisposition to osteosarcoma.

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.

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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.

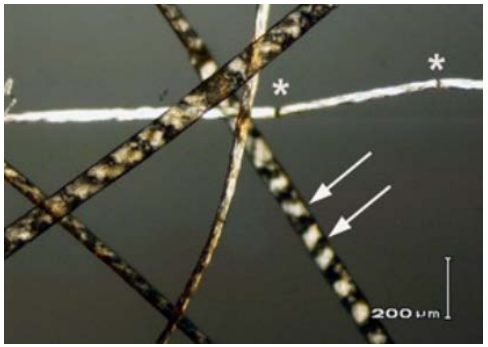
Intellectual disability, developmental delay, and motor deficits.

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.



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Werner's Syndrome

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

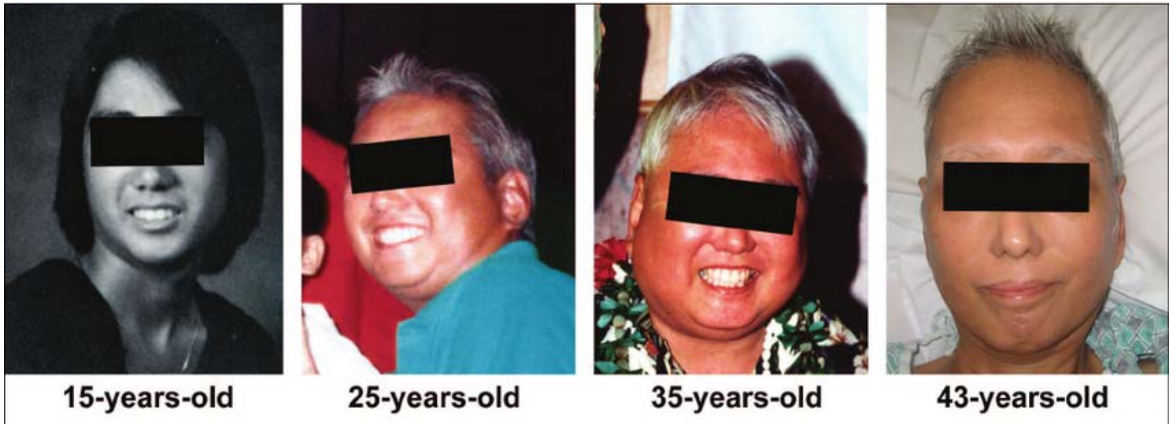
Associated with mutations in the WRN gene (chromosome 8) also known as RecQL2, which encodes a 3'-5' helicase.

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.



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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).

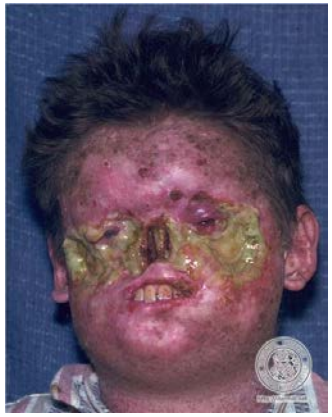
Nucleotide excision repair (NER) mechanisms are affected leading to accumulation of UV damage (thymidine dimers) and activation of proto-oncogenes.

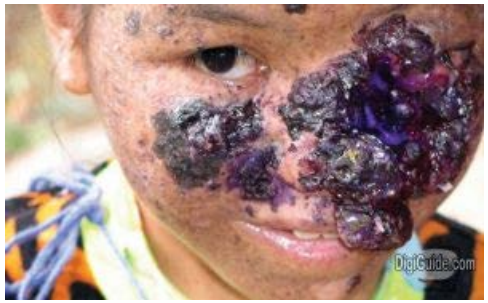
Extreme photosensitivity (“Children of the dark”), ephelides, solar keratosis, photoconjunctivitis, telangiectasias and corneal ulcers.

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.





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