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PEARLS OF LABORATORY MEDICINE

Title: Chromosome Instability Syndromes

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Characterization of chromosome instability syndromes

- Group of autosomal recessive, inherited conditions associated with failures to repair chromosome breaks
- Usually characterized by physical developmental delays resulting in small stature but very little effects on intellectual ability
- Increased risk/predisposition to develop various malignancies

Main chromosome instability syndromes

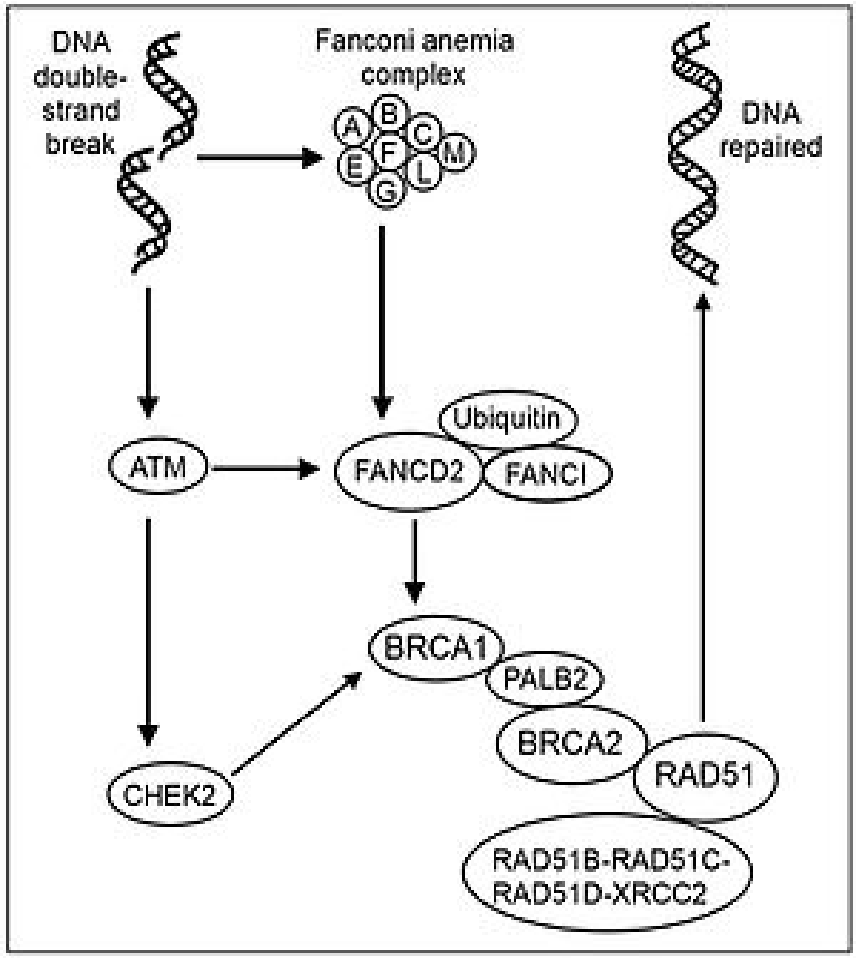
- Fanconi anemia
- Bloom syndrome
- Ataxia telangiectasia
- Nijmegen breakage syndrome
- Immunodeficiency, Centromere instability, & Facial anomalies
  - (ICF) Syndrome
- Werner syndrome
- Rothmund-Thompson syndrome

Clinical manifestations of Fanconi anemia (FA)

- Intra and inter- familial heterogeneity
  - Café au lait spots w/ hypo/hyper-pigmentation
  - Small stature w/ microcephaly or hydrocephaly
  - Urogenital abnormalities associated with renal agenesis
  - Skeletal malformations
    - Polydactyly
    - Absent radii
    - Hypoplastic thumbs
  - Gastrointestinal, gynecologic, and skin (squamous) cancers
  - Endocrine changes (hypothyroidism, pituitary dysregulation)
  - Hematological abnormalities
    - Thrombocytopenia and myelodysplasia with bone marrow failure
      - Androgen therapy can lead to hepatocellular carcinoma
    - Predisposition to malignancies including AML

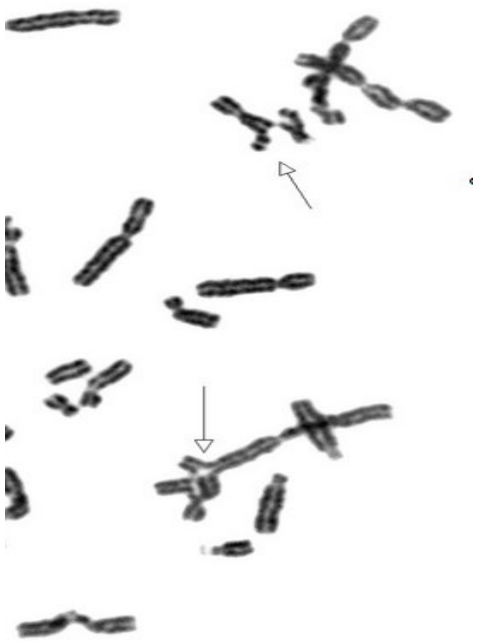
Molecular genetic characteristics of FA

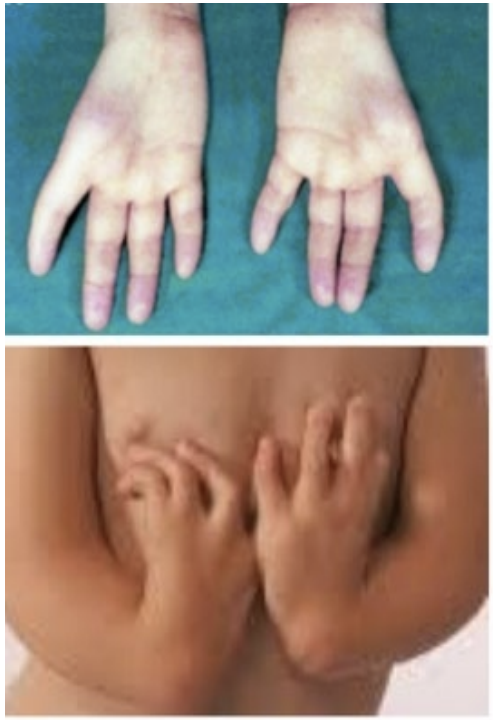
- ~97% autosomal recessive
- ~3% X-linked (*FANCB*)
- Numerous variants in > 18 FANC-genes
  - > 85 *FANCA* mutations ~ 70% of FA cases
- FA pathway normally activated to repair DNA during DNA replication
- > 95% risk of hematologic abnormality by 40 YO (> 80% mortality by 40)
  - Predominant finding is bone marrow failure, leads to AML

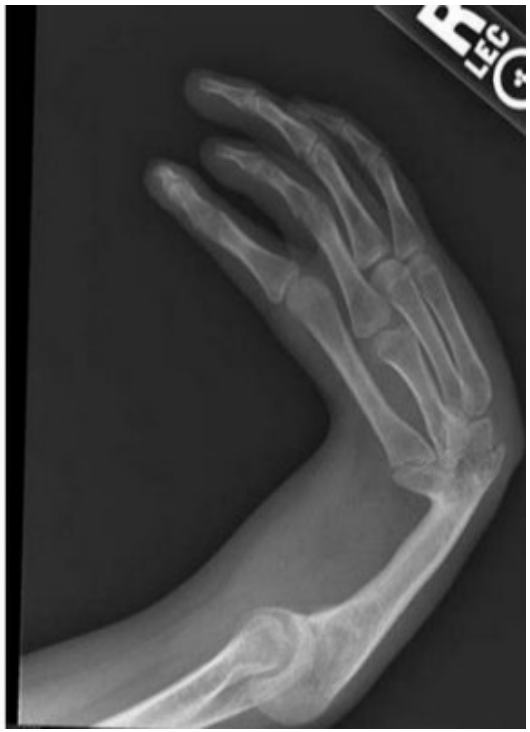


Chromosomal & limb characteristics in patients with FA

- Chromosome breakage (triradials, quadriradials)
- Hypersensitive to DNA cross-linking agents (e.g., chemotherapy)





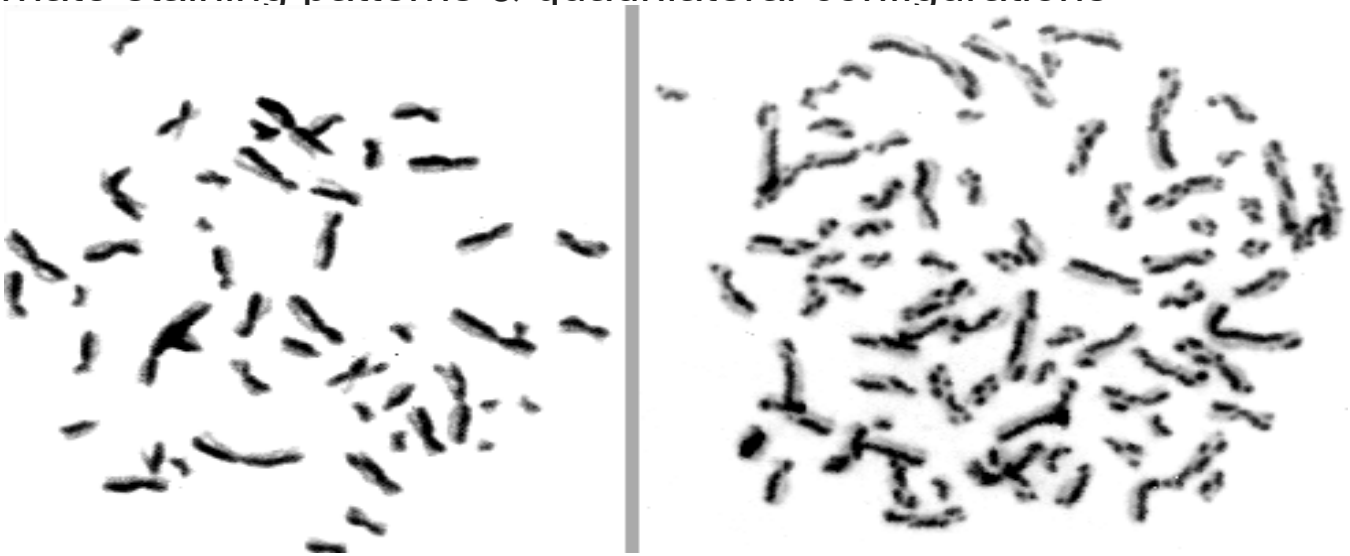


Clinical manifestations of Bloom syndrome (BLS)

- Small, proportionate body w/ micro/dolichocephaly
- Skin pigmentation; sunlight hypersensitivity
  - Telangiectasias; café au lait spots
- Generalized immunodeficiency
- Low-average intellectual ability
- Characteristic high-pitched voice
- Significant, early predisposition to many cancer types
  - Multiple, early onset cancers linked to chromosome breaks
  - High chromosome crossing over/sister chromatid exchange
  - Leukemia, lymphoma, GI adenocarcinoma, GU tumors, breast, respiratory carcinomas, sarcomas, and rarely Wilms tumor
  - Hematologic surveillance in young children is not recommended
  - Half standard doses of chemotherapy

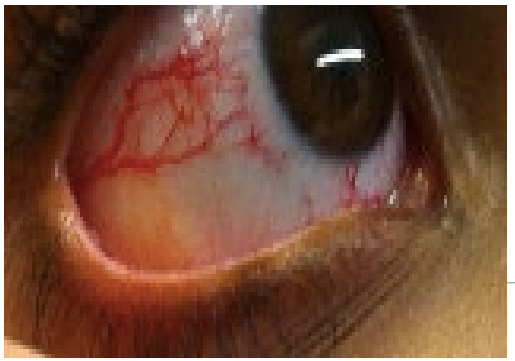
Molecular genetic characteristics of Bloom syndrome

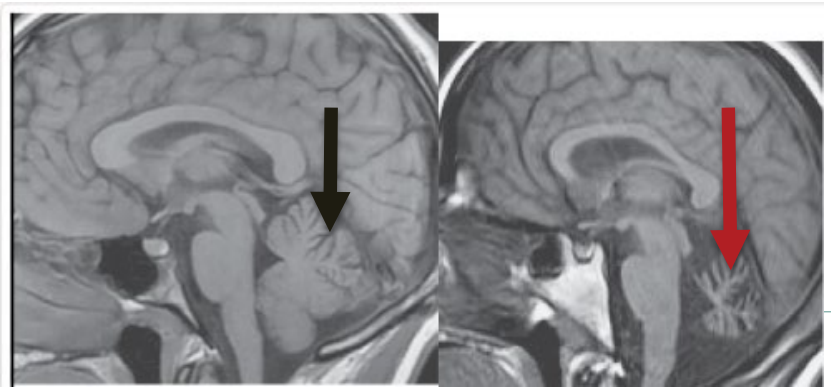
- Mode of inheritance: Autosomal recessive
- Founder mutation in Ashkenazi Jewish population:
  - 6-bp del & 7-bp ins in *BLM* at 15q26.1
- Premature truncating mutations support loss-of-function genetic model
- High sister chromatid exchange (SCE) rates (~100 SCEs/metaphase)
  - S-phase exchanges between homologous chromosome pairs
  - Alternate staining patterns & quadrilateral configurations



Clinical manifestations of Ataxia telangiectasia (A-T)

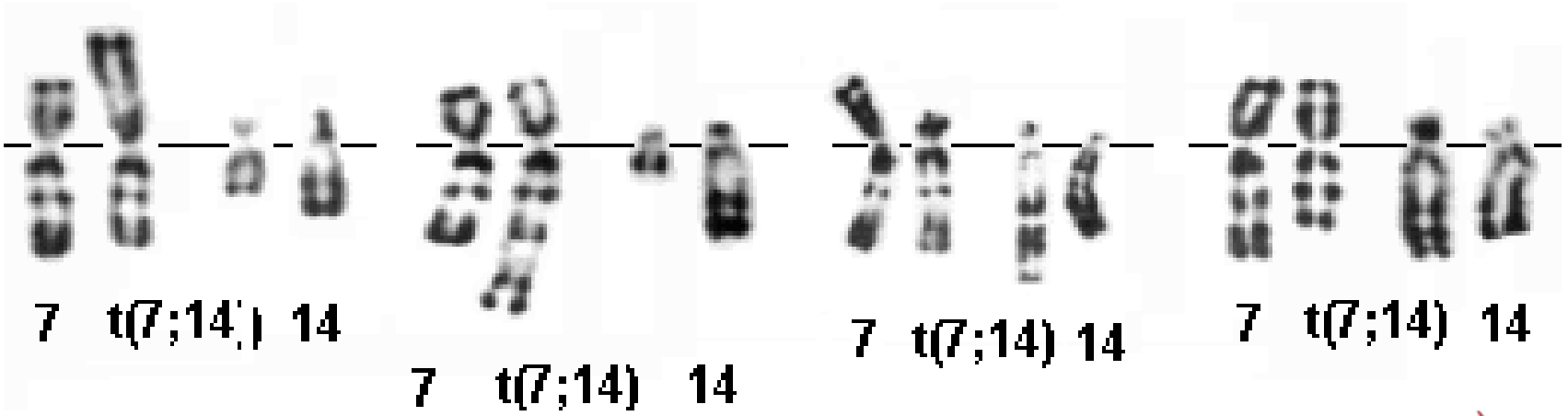
- Telangiectasias = dilated blood vessels (on skin but usually ocular)
- Progressive cerebellar degeneration with Purkinje cell depletion
- Elevated hepatic alpha-fetoprotein (> 2 YO)
- Gait and truncal ataxia at 2-3 YO; wheel chair-confined by 10 YO
- Chorea, dystonia, myoclonic jerks, tremors
- Oculomotor apraxia w/ progressive slurred speech in preschool years
- Immunodeficiency
  - low IgG, IgA, IgE, T-cells; high IgM; sometimes telomere shortening
- Historically died < 25 YO from pulmonary infections or cancer
  - Embryonic-like thymus, neurofibrillary tangles, neuronal lipofucin





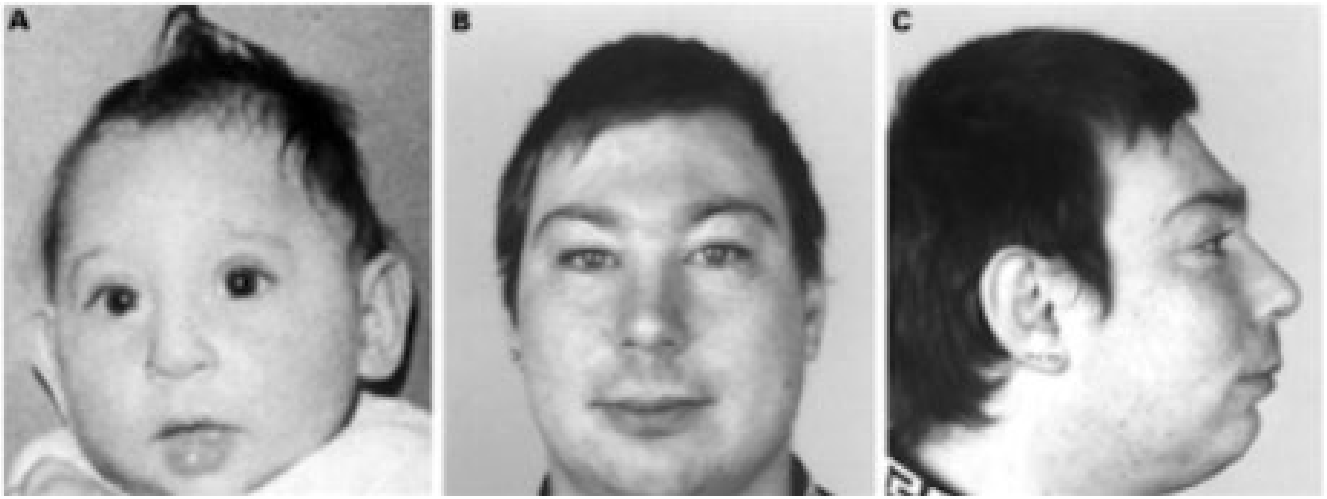
Molecular genetic characteristics of A-T

- Autosomal recessive disorder; > 400 *ATM* truncating or splice site mutations
- *ATM* at 11q22 codes for a ser/thr protein kinase activated by dsDNA breaks
- *ATM* activation phosphorylates proteins that regulate cell cycle check points
  - DNA repair and/or apoptosis normally occurs during cell-cycle arrest
  - *ATM* mutations → immunodeficiency; leukemia [t(7;14)] or lymphoma



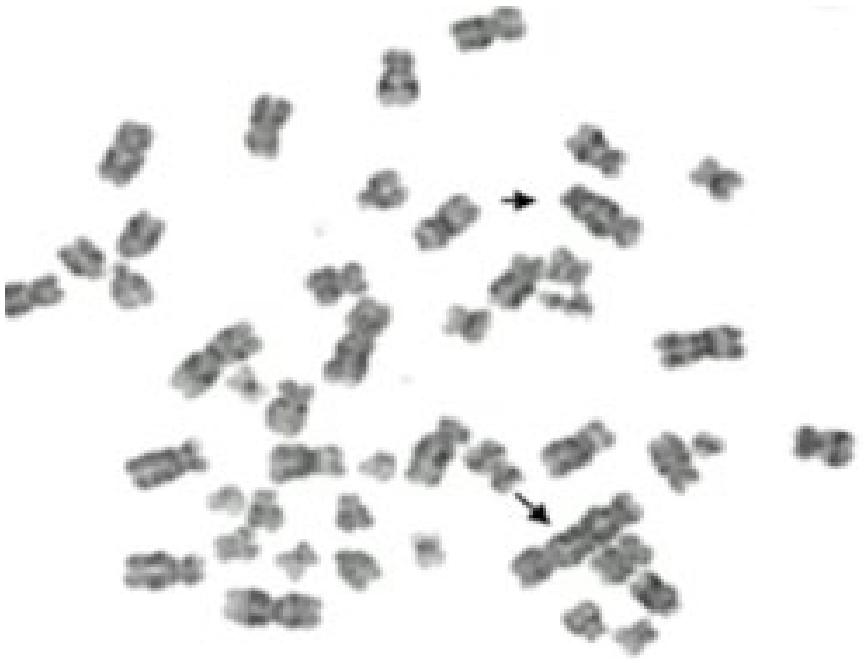
Clinical manifestations of Nijmegen breakage syndrome (NBS)

- Short stature, progressive microcephaly, beaked nose, up-slanting palpebral fissures, micrognathia
- Progressive intellectual disability starting at 3 YO
- Primary amenorrhea, infertility
- Respiratory infections (immunodeficiency; low IgA, IgG, T-cells)
- ~50X higher cancer risk than general population
  - Non-Hodgkin's lymphoma; gliomas; rhabdomyosarcoma



Molecular genetic characteristics of NBS

- Autosomal recessive; *NBN* variants at 8q21
- Most common in Polish/Slavic ancestry
- Nibrin protein normally functions in DNA repair processes
  - Non-functional nibrin → low rate of immune cell proliferation
- Spontaneous chromosome breakage and fusion (arrows); tetraploidy in marrow

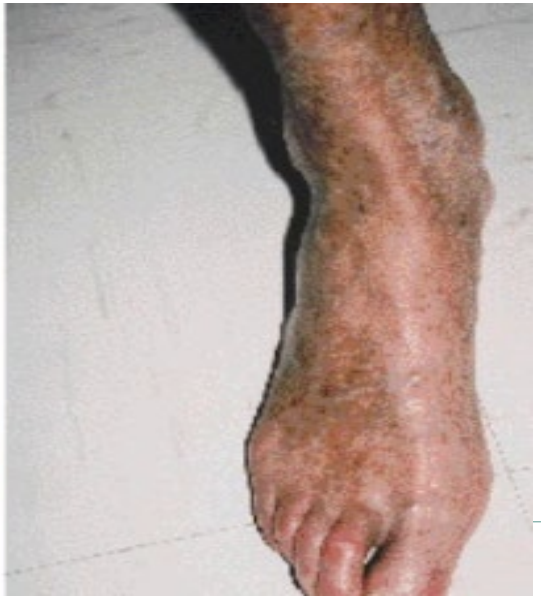


Immunodeficiency, Centromere instability, & Facial anomalies Syndrome (ICFS)

- Rearrangements in chromosomes 1, 9, & 16
- Flattened dysmorphic facial features
- Small birth weight & postural instability
- Low immunoglobulin levels → recurrent infections
  - Immunoglobulin treatment protocols
- Hypomethylation due to variants in the *DNMT3B* (DNA metyltransferase) gene

Clinical manifestations of Werner syndrome (WS)

- Failure of growth at puberty; age accelerates starting in 20s
  - Hair graying and loss
  - Hoarsening of voice
  - Thin, hardened skin → ulceration; gangrene (scleroderma-like lesions)
  - Bird-like facies; thin limbs but thick trunk (abnormal fat deposition)
  - Cataracts, atherosclerosis, & osteoporosis complicated by Type 2 diabetes
  - Lipodystrophies
  - Multiple cancers begin in 40s; survival to mid-50s

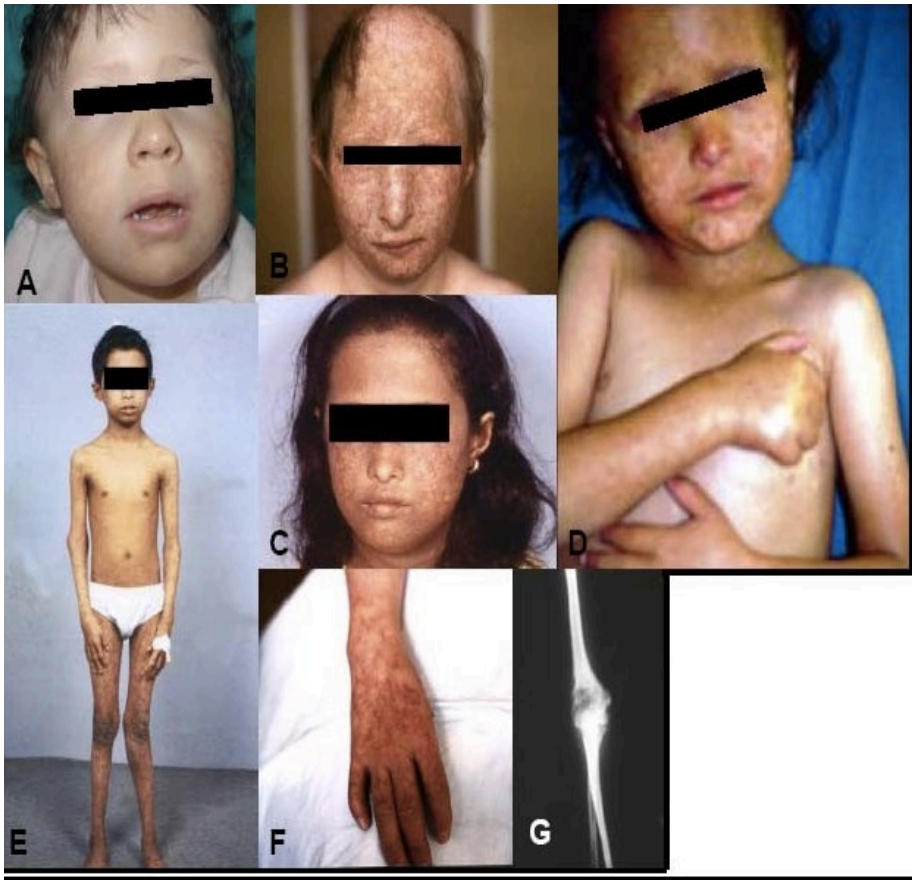


Molecular genetic characteristics of WS

- Autosomal recessive; *WRN* (*RECQL2*) at 8p12 codes for the wernin protein (WRNp) that resembles RecQ helicase, that function to repair DNA damage associated with breaks
  - Most mutations are splice site and truncating; compound heterozygous
  - WRNp maintains, repairs, and replicates DNA
  - Normally protects against oxidative damage that occurs in aging processes
  - Altered WRNp can't be transported to the nucleus, slows cell division, allows DNA damage accumulation with age-associated methylation
  - Increased rates of DNA methylation and epigenetic changes, as measured by a hypothetical molecular biomarker described as an "epigenetic clock"

Clinical and molecular genetics of Rothmund-Thompson syndrome

- Poikiloderma; premature aging
  - Skin atrophy; telangiectasia
- Sparse hair
- Dental, nail abnormalities
- Gastrointestinal disorders
- Cataracts
- Absent or malformed bones
  - Osteoporosis
  - Radial ray malformations
- Osteosarcoma in childhood
- Skin cancers
- Bialleleic pathogenic variants in *RECQL4* DNA helicase at 8q



Summary

Chromosome breakage syndromes

- Autosomal recessive inherited conditions
- Failures to repair chromosome breaks
- Dysmorphic facial features and/or other skeletal malformations
- Increased risk/predisposition to develop various malignancies

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: Nothing to disclose
- **Consultant or Advisory Role:** Nothing to disclose
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- **Honoraria:** None/nothing to disclose
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