WERNER SYNDROME

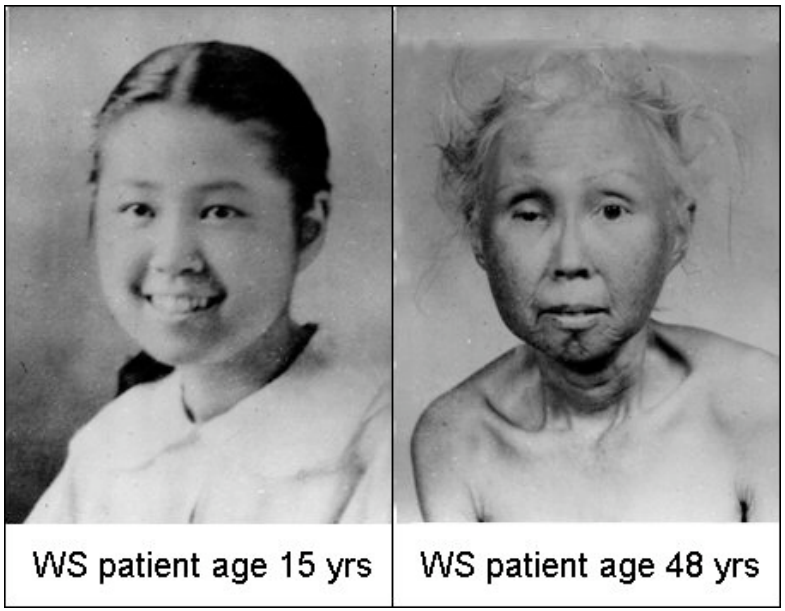
Milan Manchandia

Biochemistry 118

January 21, 2009

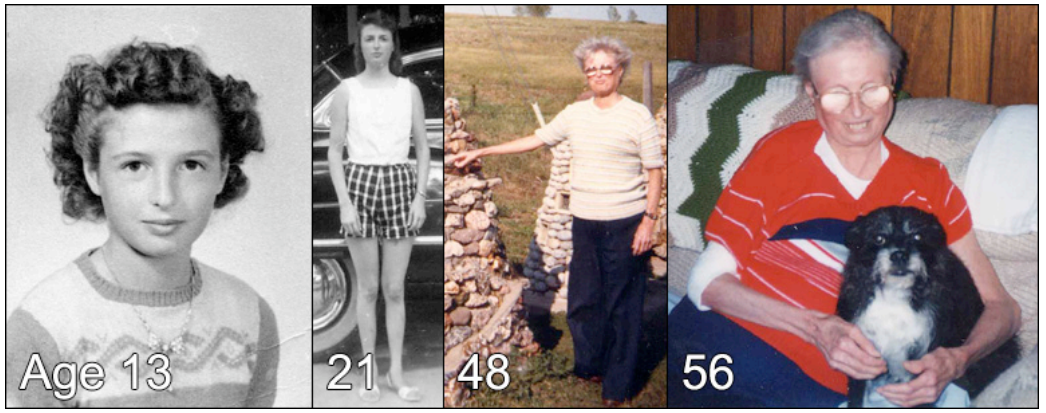
GENERAL DESCRIPTION

- Rare autosomal recessive disorder
- Appearance of premature aging
- Increased risk of developing cancer and cardio vascular disease
- Typical age of death – 48 years old
- More common in Japanese population, 1:30,000



WS patient age 15 yrs | WS patient age 48 yrs

SYMPTOMS



- Cardinal Signs and Symptoms:
  - Bilateral cataracts
  - Characteristic skin (tight, change in pigment, ulcers)
  - "Bird-like" facial appearance
  - Short stature
  - Premature graying/thinning of scalp hair
  - Affected sibling
- Further Signs
  - Type 2 Diabetes, Osteoporosis, Premature Atherosclerosis, Abnormal Voice, Flat Feet

CLASSICAL DIAGNOSIS

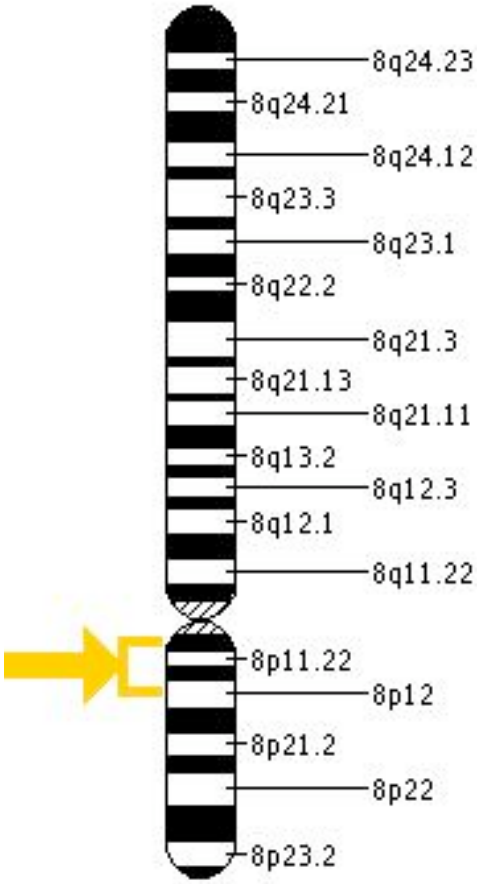
- Definite Diagnosis
  - All cardinal signs and two others
- Probable Diagnosis
  - The first three cardinal signs and any two others
- Possible Diagnosis
  - Either cataracts or skin condition and any four others
- Exclusion of Diagnosis
  - Onset of cardinal signs and symptoms before ten years old
- Increased concentration of urinary and serum hyaluronic acid
  - Testing is cumbersome and nonspecific

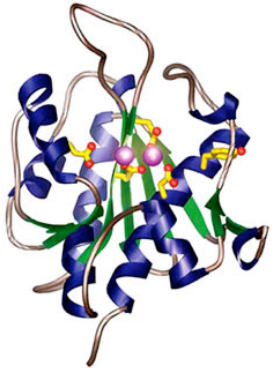
CLASSICAL TREATMENT

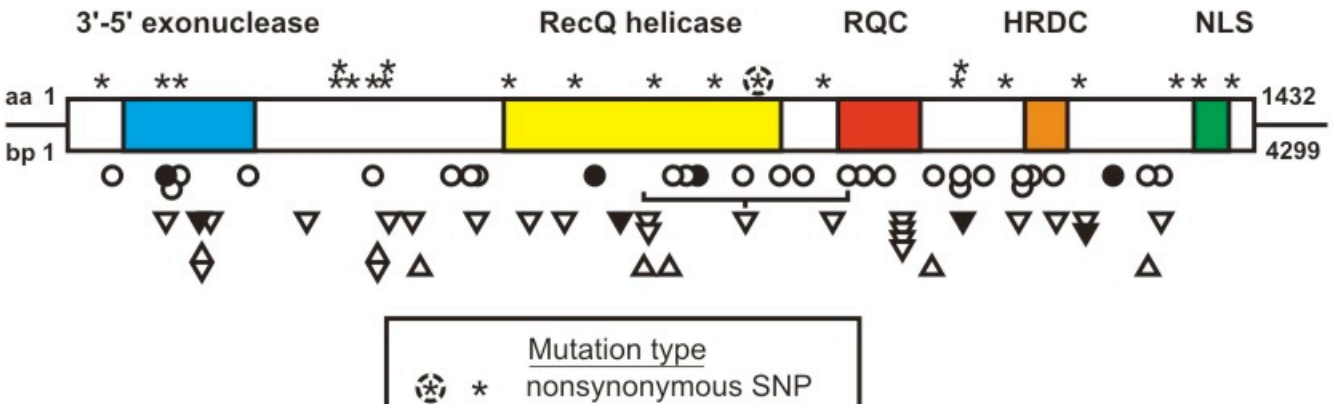
- No specific treatment to cure disease
- Aggressive treatment of skin ulcers
- Control of type 2 diabetes
- Surgical treatment of cataracts
- Prevention of Secondary Complications
  - Smoking avoidance, regular exercise, weight control
    - Reduce risk of atherosclerosis
  - Excellent skin care, trauma avoidance
- Therapies under investigation:
  - Recombinant human insulin-like growth factor for associated osteoporosis

GENETIC INFORMATION

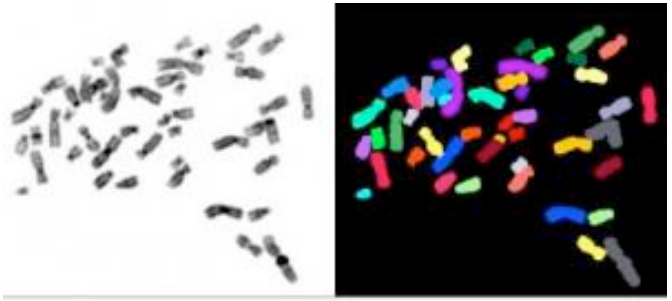
- Mutation of *WRN* gene (8p12-11.2) on short arm of chromosome 8
- Defect on gene that codes DNA helicase and 3'-5' exonuclease
- Mutations
  - Stop codon, insertions, or deletions that result in frame shift
  - Loss of nuclear localization sequence
  - Shorter mRNA and protein half-life

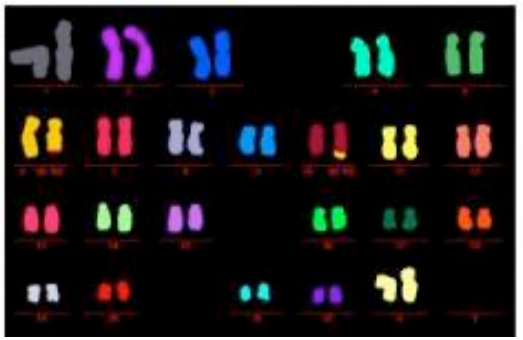






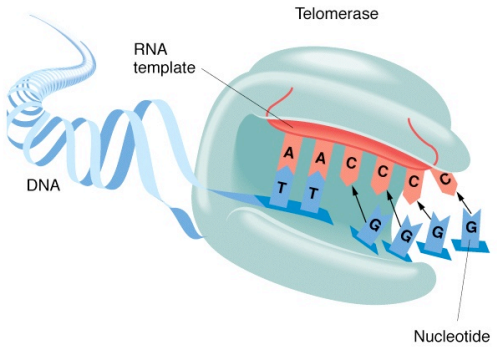
GENETIC DIAGNOSIS





- Research Testing
  - Sequential Analysis
    - Detects mutations in both alleles
  - Western blot Analysis
    - Absence of *WRN* protein
- FISH sequencing
  - Protective telomeres missing
  - Detect translocations
- Preimplantation genetic diagnosis (PGD)
  - Families in which disease has affected family member

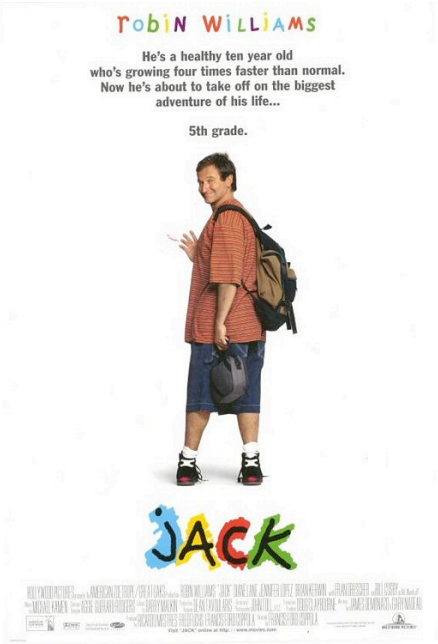
GENETIC TREATMENT



- Mechanism by which *WRN* mutations cause Werner syndrome phenotype is not clear
- Therapies Under Investigation:
  - Elongating short telomeres
    - Adding telomerase has same effect as adding functional *WRN* protein
  - Scientists have developed strain of mice exhibiting all the symptoms of Werner syndrome
- Recent publication
  - *WRN* plays important role in surveillance and protection against DNA damage induced by HQ
- Better understanding of the molecular genetics behind Werner syndrome is key to developing genetic therapy

CONCLUSION

- Treatment for Werner syndrome is very limited
- Rare disease
  - Not much incentive to find cure?
- Used as a model to study aging and cancer
- Exaggerated form of Werner syndrome:



WORKS CITED

- OMIM
- Gene Reviews
- Crabbe, L. *et al*. "Telomere dysfunction as a cause of genomic instability in Werner syndrome." Proceedings of the National Academy of Sciences. **104.7** (2007): 2205-2210.
- Ren, X *et al*. "Werner Syndrome Protein, WRN, Protects Cells from DNA Damage Induced by the Benzene Metabolite Hydroquinone." Toxicol Sci. **107.2** (2009): 367-375.