WERNER SYNDROME

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Symptoms

- Cardinal signs & symptoms

- Bilateral cataracts
- Characteristic skin (ulceration, tight skin, pigmentary alterations)
- “Bird-like” facial features (nasal bridge seems pinched)
- Short stature (lack of growth spurt during teen years)
- Premature graying/thinning of scalp hair
- Inherited: third cousin or closer, or affected sibling

- Further/Secondary signs & symptoms:

- Type 2 diabetes, osteoporosis, flat feet, atherosclerosis, secondary sexual underdevelopment and diminished infertility
**Diagnosis**

- **Definite:** all cardinal signs present + 2 others

- **Probable:** first 3 cardinal signs + any 2 others

- **Possible:** cataracts or dermatologic alterations + any 4 others

- **Exclusion:** cardinal signs + further symptoms before age 10 (except for short stature)
Treatment

- No specific treatment to cure disease

- Treatment addresses symptoms:
  - Aggressive treatment of skin ulcers
  - Control type 2 diabetes
  - Cholesterol-lowering drugs if needed
  - Surgery for ocular cataracts

- Prevention of Secondary Complications:
  - Avoidance of smoking, excess weight, & inactivity (increase the risk of atherosclerosis)
  - Skin care
+ Molecular Genetics of WS

- **Gene:** WRN
  - Only gene associated with Werner Syndrome
  - Located in short arm of chromosome 8 at position 12
  - Codes for Werner protein that is a **member of the DNA helicases family**
    - Helicases unwind DNA structures for DNA repair or replication
  - N-terminal region of the protein has **exonuclease activity**
    - Exonucleases trim broken ends of damaged DNA
  - Werner protein is needed to **maintain genomic stability** (DNA repair via unwinding or digesting intermediate DNA structures)
    - *Note- a mutation would thus easily lead to cancer*
    - Stop codon, insertions or deletions → frame shift mutations
  - **Recent finding:** needed to maintain DNA ends (telomeres)
    - Telomere dysfunction → genomic instability → cancer
Genetic Diagnosis/Testing

- Carrier testing for WRN mutations is not offered- not clinically available

- Research Testing:
  - Sequence Analysis- of WRN coding region to detect mutations
    - Results- 90% of individuals with Werner’s Syndrome showed mutations in the WRN gene
  - Western Blot Analysis- determines the effect of the mutation on the WRN protein
    - Results- majority of affected individuals with WRN mutations → absence of protein

- Preimplantation Genetic Diagnosis- available for families with affected relatives

- FISH Sequencing- found absence of protective telomeres in WS patients
**Novel Genetic Therapy**

- Therapy found while seeking to understand relationship between aging & cancer (2007)
  - Elongation of short telomeres via telomerase
  - Study added functional copy of WRN gene or a gene encoding telomerase to WS cells = equally abolished mutations/DNA damage
  - Researchers predict cancer in old people has the same basis

- Treatment is very limited

- (2011) Aging is accompanied by a decrease in WRN gene expression in human blood cells
References

- Genetics Home Reference: WRN gene
- OMIM: Werner Syndrome
- Gene Review
- Genes and Diseases
- "FISH-ing for links between cancer and aging." *Salk Institute for Biological Studies.* (2007)