Progeroid syndromes
Segmental progeroid syndromes (SPS): a group of disorders characterized by signs of premature aging in more than one organ or tissue.

Unimodal progeroid: premature aging is limited to one organ or one tissue.

Typical signs of premature aging in SPS is the premature onset of the following symptoms:

- Graying/loss of hair
- Hearing loss
- Cataract
- Scleroderma-like skin changes
- Type 2 diabetes mellitus
- Osteoporosis
- Atherosclerosis and coronary heart disease
- Various malignant tumors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Mean life-span</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werner</td>
<td>autosomal recessive</td>
<td>47-50</td>
<td>WRN (RECQL2) gene</td>
</tr>
<tr>
<td>Hutchinson-Gilford</td>
<td>autosomal dominant</td>
<td>12-15</td>
<td>LMNA gene</td>
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<tr>
<td>Cockayne</td>
<td>autosomal recessive</td>
<td>20-25</td>
<td>CSA (ERCC8) gene</td>
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<tr>
<td>Ataxia telangiectasia</td>
<td>autosomal recessive</td>
<td>20-25</td>
<td>ATM gene</td>
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<tr>
<td>Wiedemann–Rautenstrauch</td>
<td>autosomal recessive</td>
<td>Variable (&lt;1; 20-25)</td>
<td>POLR3A gene</td>
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<tr>
<td>Myotonic dystrophy type 1</td>
<td>autosomal dominant</td>
<td>48-55</td>
<td>Trinucleotide repeat expansion in DMPK gene</td>
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</tbody>
</table>
**Hallmarks of WS**

**Incidence:** 1:500,000 - 1:1,000,000

Most tissues and organs are affected.

Pathology: short stature, graying and loss of hair, cataracts, bone deformities, lack of subcutaneous fat. Diabetes, atherosclerosis, osteoporosis, malignancies.

Cause of death: myocardial infarction.

**Spectrum of mutations in the WRN gene**

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**Hallmarks of HGPS**

**Incidence:** 1:6,000,000.

Most tissues and organs are affected.

Pathology: dwarfism wrinkled/aged-looking skin, baldness, and a pinched nose.

Respiratory, cardiovascular, and arthritic conditions.

Cause of death: myocardial infarction.

**De-novo mutation in the LMNA gene**

Activation of a cryptic splice site

Prelamin A processing pathway

HGSP

- Mature lamin A
- partially processed lamin A (progerin)

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**Loss of WRN protein**
HGSP: deregulation of nuclear functions

Lamin A contribute to the regulation of cell structure and function

Lamin A mutations and disease: laminopathies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dominant</th>
<th>Recessive</th>
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</thead>
<tbody>
<tr>
<td>EDMD2/3</td>
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<td>✓</td>
</tr>
<tr>
<td>LGMD1B</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CMD1A</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MDC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>H-HS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HGPS</td>
<td>✓ (rare)</td>
<td>✓</td>
</tr>
<tr>
<td>CMT2A</td>
<td>✓ (rare)</td>
<td>✓</td>
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<tr>
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<td>✓</td>
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<tr>
<td>RD</td>
<td>✓</td>
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</tr>
</tbody>
</table>

chromatin organization
DNA damage response
telomere length homeostasis
nucleocytoplasmic transport
antioxidant response
DNA replication
Gene expression
Lamin A maturation pathway: a biomarker of biological aging?

Hdf from young healthy donor

Hdf from old (89y) healthy donor

Hdf (+ ectopically expressed lamin A)

Prelamin A processing pathway

FT
ZMPSTE24/RCE1
ICM
ZMPSTE24
Mature lamin A

Toxic intermediates

% cells with Lamin A aggregates

control F-lamin A Unl-lamin A young ppi

p = 0.03
Lamin A maturation pathway: a therapeutic target for physiological aging?

1. Disease-linked mutation

LMNA (1824 C>T) → progerin → Accelerated aging (progeria)

2. Perturbation of normal prelamin A metabolism in physiological aging

Age-dependent increase in mis-splicing

Nucleus malfunction

Age-dependent decrease in enzymatic activity

ZMPSTE24
RCE1
ICM

muscular dystrophy
osteoporosis
lipodystrophy
diabetes
cardiomyopathy
atherosclerosis

healthy
Werner syndrome
(adult onset progeria)

loss-of function mutations in the Werner syndrome gene, which encodes for a protein with helicase and exonuclease activities (WRN)

(DNA repair, transcription ?)

DNA replication: lagging strand synthesis

Genetic instability

- Prolonged S-phase of the cell cycle.
- Genetic instability-chromosome deletions and translocation (variegated translocation mosaicism).
- Altered telomere length homeostasis.
- WRN deficiency results in the loss of telomeres replicated by lagging strand synthesis and the formation of extrachromosomal telomeric circles.

telomeres

Other genomic loci?
Three motifs are the most common sequence features enriched in WRN ChIP peaks

- WRN binding sites are repetitive elements/low-complexity motifs.
- Repetitive DNA sequences are a major threat to genome stability often driving chromosome rearrangements and disease.
- Repetitive sequences represent a challenge to the replication machinery because they are prone to form stable secondary (non-canonical) structures.
- Maintaining the stability of loci with repetitive sequences is critical to overall cellular fitness and lifespan, but this weakness be exploited to generate replication catastrophe in cancer cells.

WRN was discovered as a completely novel selective vulnerability in Microsatellite Instability (MSI) cancer (Chan EM et al., Nature 2019; Lieb S et al., eLife 2019; Kategaya L et al., iScience 2019; Behan FM et al., Nature 2019).

In MSI cancer cells, WRN is required for DNA replication through (TA) n dinucleotide repeats scattered throughout the genome (van Wietmarschen N et al., Nature 2020)
WRN binding sites correlate with structural variants in the human genome

- Structural variants (SV) include cytogenetically detectable and submicroscopic Copy Number Variants (CNVs; deletions, duplications, and insertions rearrangements, such as inversions and interchromosomal and intrachromosomal translocations).

- SVs are present in every human genome and can affect molecular and cellular processes, regulatory functions, 3D structure and gene expression.
Progeroid syndromes: a window into biological aging

- Lamins regulate many fundamental nuclear processes thereby playing a critical role in cell homeostasis.

- Prelamin A processing pathway is tightly regulated, and small perturbations can alter the balance between health and disease.

- WRN contributes to telomere length homeostasis, thereby affecting the onset of replicative senescence.

- WRN maintains the stability of repetitive elements across the human genome, thus influencing phenotypic variation and disease.
THANK YOU!

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