Premature human aging: t he progerias

Reading:
Genetic alterations in accelerated ageing syndromes Do they play a role in natural ageing? Monika Puzianowska-Kuznicka. Jacek Kuznicki. 2005. IJBCB, 37; 947–960

Progeria OMIM entries

A&S300-002 Jim Lund

Progeria

Definition:

- A disease characterized by symptoms of premature aging.
- Hutchinson-Gilford syndrome

Progerias as models for aging

Are progerias premature aging or a disease condition?

How well do they parallel aging?
One aspect or every aspect?

Many diseases lead to the disruption of some biological process--but aren't aging.

Hutchinson-Gilford syndrome

Hutchinson-Gilford syndrome

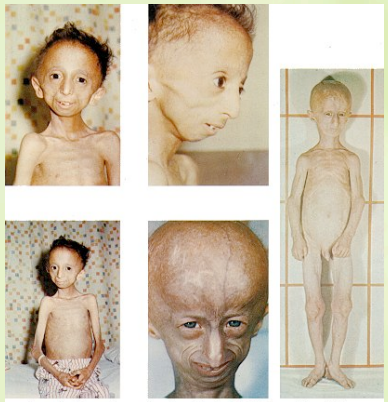
- First described by Jonathan Hutchinson in 1886. Hastings Gilford gave it the name progeria and described it in 1904.
- Hutchinson-Gilford progeria syndrome is an exceedingly rare disorder characterized by precocious senility of a striking degree. Death from coronary artery disease is frequent and may occur before 10 years of age.

Hutchinson-Gilford syndrome
Clinical Features

- Slow growth, dwarfism.
- Lack of hair
- Disproportionately large head
- 'Pinched' facial features
- Lipodystrophy (almost complete absence of subcutaneous fat).
- Incomplete extension at the knees and elbows indicating stiffness of joints.
- Coronary artery disease.
- Generally a senile appearance

By 10 patients start turning grey, die in teens typically of heart disease.

Hutchinson-Gilford syndrome



Progeria: Premature aging. Usually die at 10-15 yrs.of heart failure.
SS Gellis, M Feingold. Atlas of Mental Retardation Syndromes. 1968.

Hutchinson-Gilford syndrome

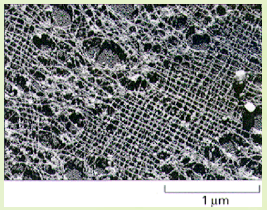
- Inheritance: both autosomal dominant and autosomal recessive cases have been reported, the classic cases are autosomal dominant.
- Incidence: 1 in 8,000,000

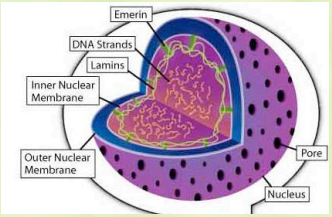
Hutchinson-Gilford syndrome gene

- Gene isolated: Eriksson et al. (2003)
- Caused by mutations in the lamin A gene.
  - Gene symbol: **LMNA**.
- Lamins are structural protein components of the nuclear lamina, a protein network underlying the inner nuclear membrane that determines nuclear shape and size. The lamins constitute a class of intermediate filaments

Lamins

- Nuclear lamina - a protein network underlying the inner nuclear membrane that determines nuclear shape and size.
- Major components: Lamin A, B, and C.
- Lamins are a class of intermediate filaments.





Cloning and molecular genetics

- The gene was initially localized to chromosome 1q by observing 2 cases of uniparental isodisomy of 1q, and 1 case with a 6-Mb paternal interstitial deletion.
- Eighteen of 20 classic cases harbored the identical de novo single-base substitution, a C-to-T transition resulting in a silent gly-to-gly change at codon 608 within exon 11
  - Mutations activate a cryptic splice site within exon 11 of the lamin A gene, resulting in production of a protein product that deletes 50 amino acids near the C terminus.

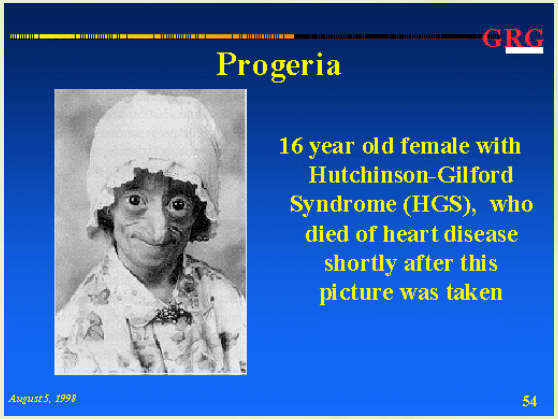
Model for aging?

Differences between Hutchinson-Gilford syndrome and aging.

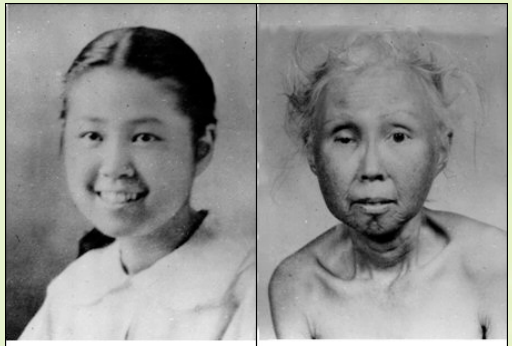
Not part of Hutchinson-Gilford syndrome:

- Males don't develop prostate problems.
- No increased risk of cancer or cataracts.
- High blood pressure is rare.
- Diabetes rare.
- Don't get Alzheimer's disease or suffer mental degeneration.

Hutchinson-Gilford syndrome



Werner's syndrome



WS patient age 15 yrs | WS patient age 48 yrs

Werner's syndrome
Clinical features

- Also called adult progeria.
- Scleroderma-like skin changes, especially in the extremities (hardening and tightening of the skin)
- Cataracts
- Subcutaneous calcification
- Premature arteriosclerosis
- Diabetes mellitus
- Cancer
- A wizened and prematurely aged facies.

Werner's syndrome

- Inheritance: autosomal recessive
- Incidence: 1 in 1,000,000
- In Japan, the syndrome occurs more often, affecting between 1 in 20,000 and 1 in 40,000 people.

Werner's syndrome: cellular features

Normal human fibroblasts achieve approximately 60 population doublings in culture.

Werner syndrome cells usually achieve only about 20 population doublings.

(lower Hayflick limit).

Werner's syndrome gene

- Gene isoloated: Yu et al. (1996)
- Gene: WRN/RECQL2, a DNA helicase.
  - homolog of the E. coli RecQ DNA helicase.
  - Mutations are typically loss of function/null mutations.
- Some patients have LMNA mutations (autosomal dominant).

Model for aging?

Differences between Werner's syndrome and aging.

Not part of Werner's syndrome:

- Prostate problems (other cancers common)
- High blood pressure
- Stroke
- Don't get Alzheimer's disease or suffer mental degeneration.

Many diseases have progeriod aspects:

Premature loss or graying of hair: 18+ genes

Early cardiovascular disease: 30+ genes.

Early senility: 50+ genes.

Not good general models for aging.

Down syndrome: a progeria

Caused by trisomy 21.
Incidence: 1 in 700.

- Premature greying/hair loss
- Early vascular disease
- Early onset Alzheimer's disease: universal by 35-40.
- But no: prostate or breast cancer, high blood pressure, wrinkles, osteoporosis, cataracts.

Diabetes has features of progeria

Progeriod features:

- Cataracts
- Atherosclerosis
- Heart attacks
- Strokes
- Lung and joint stiffening

Major causative factor is Advanced Glycosylation Products (AGEs) damage.