Hutchinson-Gilford Progeria Syndrome

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Introduction and History

- The Hutchinson-Gilford Progeria Syndrome (Progeria): fatal disease that causes rapid aging
- Only 1 in 8 million have this disease
- First appearance: Hutchinson(1886)
- Second appearance: Gilford (1904)
- Only roughly 60 cases have been reported since: (Debrusk 1972, Brown et al. 1985 & 1986)
- Erikkson et al. 2003—f rst research done to show actual causes and effects

Research of Erikkson et. al (2003)

1. Out of 23 progeria, he found that 20 had a *de novo* mutation in LMNA gene(codes for nuclear Lamina A)
2. 18 out of 20: GGC→GGT

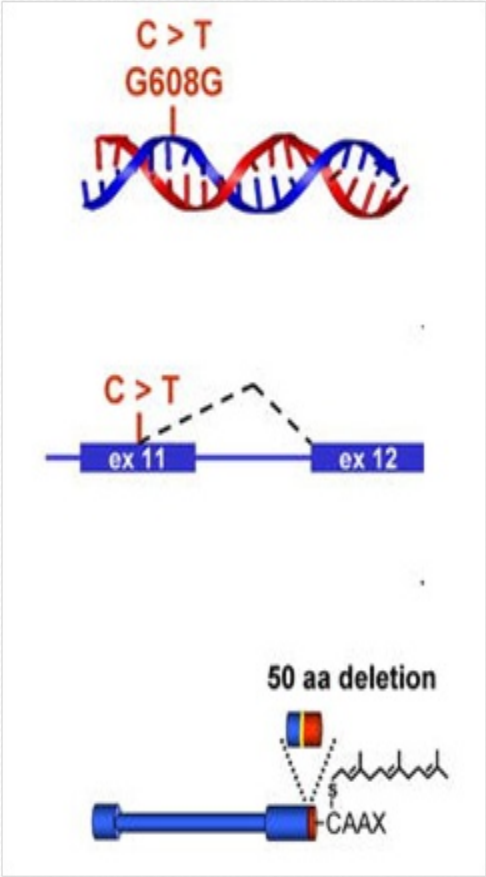
   1 out of 20: GGC→AGC

   1 out of 20: GAG→AAG

   The causes of Progeria in the other three cases are unknown
3. Creation of splice site

Mechanisms of mRNA Splicing

- Introns vs. Exons
- Donor acceptor pairs: GT-AG, GC-AG, AT-AC, and GT-GG. (Fong et al. 2006). The base pair progressions, GT, GC, and AT have the potential to set of a splice site.
- The splice site signals the excision of genetic information, leading to a deletion of 150 bps, and 50 amino acids.



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Truncated Lamina A: Progerin

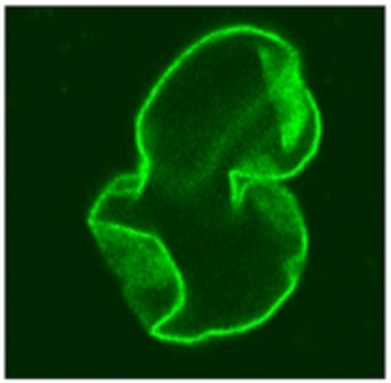
Normal Wild-type Lamina contains two modif cations (attachments): the farsynal group and the terminal group. Removal of two groups→successful integration into Nuclear Membrane.

Truncated Lamina A (Progerin): does not have terminal group. Cannot successfully integrate, and messes up integration of future Laminas.

Lamina keeps stable structure

And Progerin ruins it; nuclear lamina

Becomes lobular. Funky Nuclear Lamina →

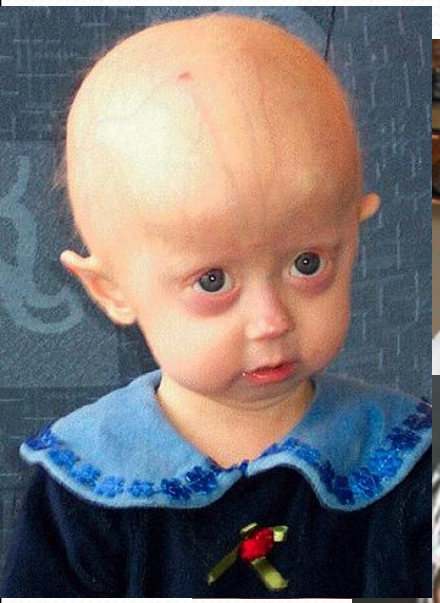


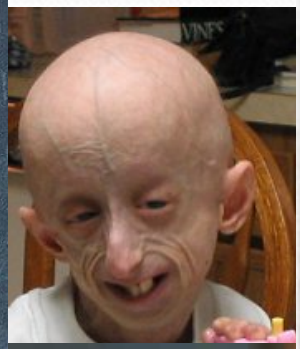
Reverse Transcriptase Polymerase Chain Reaction

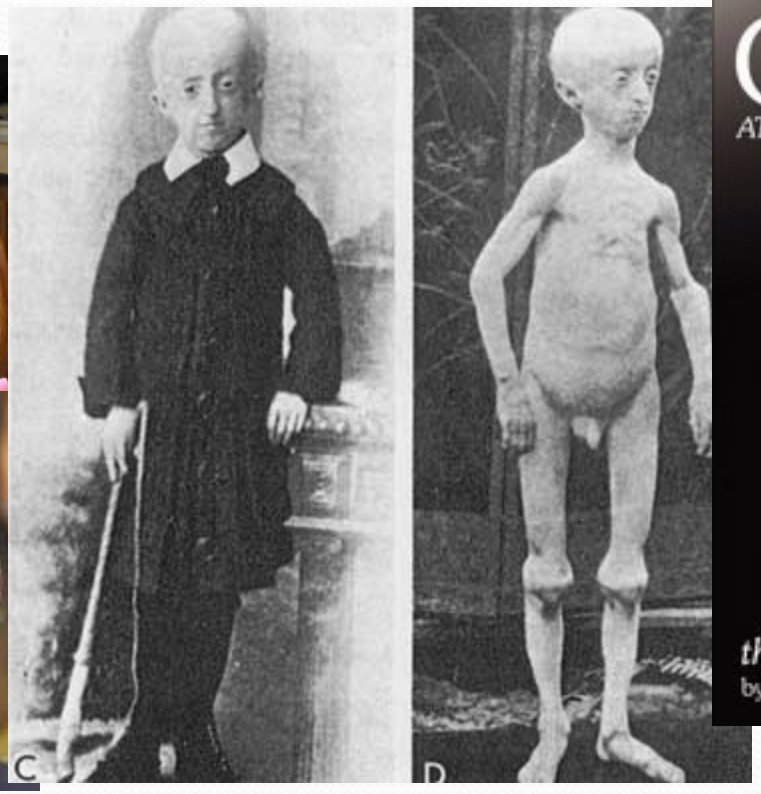
- mRNA is copied into DNA by using a oligo dT primer. Certain Heat-Stable DNA polymerase known as Taq polymerase is used for further transcription
- Denaturization of DNA
- mRNA primers added to separate DNA strands. Taq polymerase starts to add on base pairs from the RNA primers. Total of 4 strands from 1 mRNA.

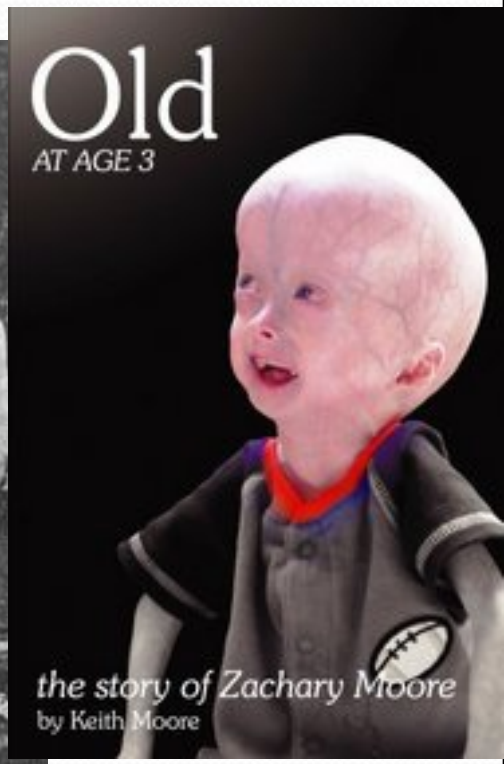
Effects

- Most prevalent of rapid aging symptoms: hair loss early , bulging out eyes, visible veins on body and head, Egg-shaped head, atheroscleosis, deformed bones, calcium loss, and other growth deformities









Treatment
Macro and Molecular

Macro:

- Giving increased Growth hormone
- Give medication to reduce fat buildup in the Coronary Arteries, or coronary bypass surgery
- Cao et al. (2011): rapamycin abolished nuclear blebbing, delayed the onset of cellular senescence, and enhanced the degradation of progerin in HGPS cells. (ONIM)

Molecular:

- Glynn and Clover (2005): farnesylation inhibition (ONIM)

Conclusion: Recap

- Progeria is a disease that causes rapid aging and is caused by a base-pair substitution in the LMNA gene.
- Effects include abnormally projecting eyes and other growth defects
- Treatments include FTI's that inhibit the progerin from reaching nucleus, increased supplements of Gh and calcium, and medication to reduce effects of atherosclerosis

Thank You
Questions?

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