



PROGERIA: A REVIEW

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ABSTRACT

Progeria or Hutchinson–Gilford progeria syndrome is a rare genetic disorder characterized by dramatic premature aging and accelerated cardiovascular disease. It is almost never passed on from parent to child. Progeria is almost always caused by de novo point mutation in the lamin A gene that activates a cryptic splice donor site, producing a truncated mutant protein termed “progerin.” Progeria shows characteristic facial appearance including prominent eyes, thin nose with a beaked tip, thin lips, a small chin, and protruding ears, severe hardening of the arteries beginning in childhood. In the past, doctors had to base a diagnosis of progeria solely on physical symptoms but progeria research foundation establishes the Progeria cell and tissue bank to assist in further research and diagnostic process. Aspirin may help prevent atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Vitamin supplementation, Fluoride supplements are recommended. A Study of Zoledronic acid, Pravastatin, and Lonafarnib for Patients with Progeria is ongoing, it is under phase II.

Keywords: Progeria, Progerin, Aspirin, Pravastatin, Atherothrombotic.

INTRODUCTION

Progeria also known as "Hutchinson–Gilford Progeria Syndrome" (HGPS) is a rare premature aging disorder that belongs to a group of conditions called laminopathies which affect nuclear lamins.¹ Mutations in two genes, LMNA and ZMPSTE24, have been found in patients with HGPS. The p.G608G LMNA mutation is the most commonly reported mutation.² The word progeria comes from the Greek words "pro" meaning "before", and "gêras" meaning "old age". The disorder has very low incidences and occurs in an estimated 1 per 8 million live births. Progeria subjects have normal to above- average intelligence. The median age of death is 12 years.³ Those born with progeria typically live to their mid teens and early twenties. It is a genetic condition that occurs as a new mutation (de novo), and is rarely inherited. Although the term progeria applies strictly speaking to all diseases characterized by premature aging symptoms, and is often used as such, it is often applied specifically in reference to Hutchinson-Gilford Progeria Syndrome.

Scientists are particularly interested in progeria because it might reveal clues about the normal process of aging. Progeria was first described in 1886 by Jonathan Hutchinson.⁴ It was also described independently in 1897 by Hastings Gilford. The condition was later named Hutchinson-Gilford Progeria Syndrome (HGPS).⁵

SIGNS AND SYMPTOMS

Children with progeria usually develop the first symptoms during infancy. The earliest symptoms include failure to thrive and a localized scleroderma-like skin condition. As a child ages past infancy, additional conditions usually become apparent around 18–24 months. Limited growth, full-body alopecia, and a distinctive appearance (small face and jaw, pinched nose) are all characteristics of

progeria. Signs and symptoms of this progressive disease tend to get worse as the child ages. Later, the condition causes wrinkled skin, atherosclerosis, kidney failure, loss of eyesight, hair loss, and cardiovascular problems.⁶ Scleroderma, a hardening and tightening of the skin on trunk and extremities of the body, is prevalent. People diagnosed with this disorder usually have small, fragile bodies, like those of elderly people. The face is usually wrinkled, with a larger head in relation to the body, a narrow face and a beak nose. Prominent scalp veins are noticeable (made more obvious by hair loss), as well as prominent eyes. Musculoskeletal degeneration causes loss of body fat and muscle, stiff joints, hip dislocations, and other symptoms generally absent in the non-elderly population. Individuals usually retain normal mental and motor development.⁷

Children with Progeria are born looking healthy. When they are about 10 to 24 months old, features of accelerated aging start to appear. Signs of Progeria may include:

- Slowed growth, with below-average height and weight
- Loss of body fat
- Hair loss (alopecia), including eyelashes and eyebrows
- A narrowed face and beaked nose⁸
- Hardening and tightening of skin on trunk and extremities (scleroderma)
- Head disproportionately large for face (macrocephaly)
- Thin lips
- Visible veins
- Prominent eyes



- Small lower jaw (micrognathia)
- High-pitched voice
- Delayed and abnormal tooth formation
- Diminished body fat and muscle
- Stiff joints
- Hip dislocation
- Insulin resistance
- Irregular heartbeat
- Open soft spot (fontanelle)⁹

Although they may come from varying ethnic backgrounds, children with Progeria have a surprisingly similar appearance. Progeria patients generally die between the ages of 8 and 21 - with the average age being 13.

CAUSES

The follow list shows some of the possible medical causes of Progeria that are listed by the Diseases Database:

- Cockayne syndrome
- Werner's syndrome¹⁰
- Lison syndrome
- de Barsy syndrome¹¹
- Xylosylprotein 4-beta-galactosyltransferase deficiency
- Geroderma osteodysplastica
- Acrogeria
- Hutchinson-Gilford progeria syndrome
- Wiedemann-Rautenstrauch syndrome¹²

MUTATION IN LAMIN A CAUSES PROGERIA

Originally thought to be an autosomal-recessive disorder, more recent evidence has identified the genetic basis for progeria to be a single nucleotide mutation with autosomal-dominant expression.¹³⁻¹⁶

Lamins are type V intermediate filament proteins and have a short N-terminal "head" domain, an alpha-helical "central rod" domain, and a globular tail domain. Lamins are classified as either A or B type according to their primary sequence, expression pattern, and biochemical properties. B-type lamins are expressed in all cells during development and in adult animals, whereas A-type lamins are expressed in differentiated cells. The LMNA gene encodes three A-type lamins: lamin A (LA), lamin C, and lamin A delta-10. Lamin A contains a C-terminal CAAX box, which undergoes methyl esterification and farnesylation.¹⁷ In the process of LA maturation, the C-terminal 18 residues, which include the modified C-terminal cysteine, are removed in two specific cleavage steps. The most frequent LMNA mutation in Hutchinson-Gilford progeria syndrome is a nucleotide substitution at position 1824, C-to-T, resulting in a silent gly-to-gly mutation at codon 608 (G608G) within exon 11 of the LMNA gene. This predicts a deletion of 50 basepairs of

prelamin A near the C terminus. Low levels of both the mutant mRNA and the mutant protein, LA delta-50, are expressed in fibroblasts derived from Hutchinson-Gilford progeria syndrome patients.¹⁸

Table 1: Comparison between a normal cell and a progeria cell

STEPS IN NORMAL CELL	STEPS IN PROGERIA CELL
The gene LMNA encodes a protein called prelamin A	The gene LMNA encodes a protein called prelamin A
Prelamin A has a farnesyl group attached to its end	Prelamin A has a farnesyl group attached to its end
Farnesyl group is removed from prelamin A	Farnesyl group remains attached to prelamin A
Normal form called PRELAMIN A	Abnormal form of prelamin A called PROGERIN
Prelamin A is not anchored to the nuclear rim	Progerin is anchored to the nuclear rim
Normal state of the nucleus	Abnormally shaped nucleus

In addition, Hutchinson-Gilford progeria syndrome cell nuclei frequently display irregular shapes. In normal conditions, the LMNA gene encodes a protein called prelamin A, which leads to the lamin A form. There is a farnesyl group attached to the carboxyl-terminus of its structure. Farnesyl molecule allows prelamin A to be anchored to nuclear rim, and then it is removed. Before the late 20th century, research on progeria yielded very little information about the syndrome. In 2003, the cause of progeria was discovered to be a point mutation in position 1824 of the LMNA gene, replacing cytosine with thymine, creating a truncated form, progerin, of the prelamin A protein whose further processing is abnormal. Normal lamin A is a major structural protein of the nuclear lamina of the nucleus (along with lamin C); when LMNA is mutated, farnesyl group cannot be removed and progerin does not integrate into this structure and accumulates, disrupting it. This is when HGPS appears. Since the nuclear lamina participates in organizing chromatin and supporting the nuclear envelope; this disrupts the human cell nucleus as a whole, limiting the ability of the cell to divide. Then, the appearance of affected nuclei is like bubbles or a cluster of grapes. Progerin may also play a role in normal human aging, since its production is activated in senescent wild type cells.¹⁹

MODELS USED FOR PROGERIA

1. Mouse Model of Progeria

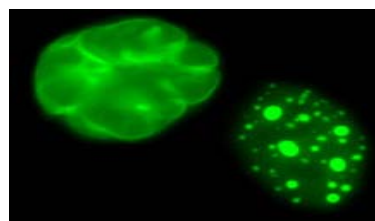


Figure 1: Untreated cells from children with the genetic disease progeria (left) compared to similar cells treated with farnesyltransferase inhibitors (FTIs). In the test tube, FTIs reverse the nuclear damage caused by the disease.

Three different mouse models have begun to shed some light on HGPS pathogenicity. Each model supports the link between LMNA and progeria. A LMNA knockout mouse resulted in a mouse that had severe postnatal growth delays, muscular dystrophy, and nuclear abnormalities. A mouse model of progeria exists, though in the mouse, the LMNA prelamin A is not mutated. Instead, ZMPSTE24, the specific protease that is required to remove the C-terminus of prelamin A, is missing. Both cases result in the buildup of farnesylated prelamin A on the nuclear membrane and in the characteristic nuclear LMNA blebbing. Fong et al. use a farnesyl transferase inhibitor (FTI) in this mouse model to inhibit protein farnesylation of prelamin A. Treated mice had greater grip strength and lower likelihood of rib fracture and may live longer than untreated mice.²⁰

This method does not directly "cure" the underlying cause of progeria. This method prevents prelamin A from going to the nucleus in the first place so that no prelamin A can build up on the nuclear membrane, but equally, there is no production of normal lamin A in the nucleus. Lamin A does not appear to be necessary for life; mice in which the LMNA gene is knocked out show no embryological symptoms (they develop an Emery–Dreifuss muscular dystrophy-like condition postnatally). This implies that it is the build up of prelamin A in the wrong place, rather than the loss of the normal function of lamin A, that causes the disease.

It was hypothesized that part of the reason that treatment with an FTI such as alendronate is inefficient is due to prenylation by geranylgeranyltransferase. Since statins inhibit geranylgeranyltransferase, the combination of an FTI and statins was tried, and markedly improved "the aging-like phenotypes of mice deficient in the metalloproteinase Zmpste, including growth retardation, loss of weight, lipodystrophy, hair loss, and bone defects".

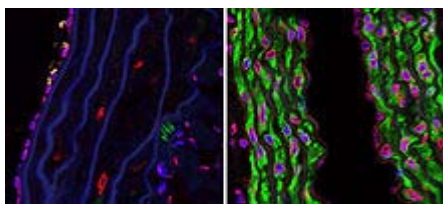
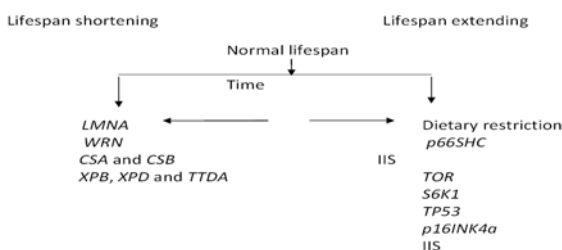


Figure 2: Confocal microscopy photographs of the descending aortas of two 15-month-old progeria mice, one untreated (left picture) and the other treated with the farnesyltransferase inhibitor drug tipifarnib (right picture). The microphotographs show prevention of the vascular smooth muscle cell loss that is otherwise rampant by this age. Staining was smooth muscle alpha-actin (green), lamins A/C (red) and DAPI (blue). (Original magnification, x 40)



2. Genetic models for progerias and enhanced longevity

Mutations in lamin A/C (*LMNA*), Werner syndrome ATP-dependent helicase (*WRN*), Cockayne syndrome protein A (*CSA*; also known as *ERCC8*) and *CSB* (also known as *ERCC6*), and several DNA repair genes, such as xeroderma pigmentosum group B complementing (*XPB*; also known as *ERCC3*), *XPD* (also known as *ERCC2*) and *TTDA* (also known as *GTF2H5*), are associated with diseases that resemble premature ageing in humans. To date, there is little, if any, known overlap of genes associated with progerias with genes that are known to extend longevity in mammals, such as target of rapamycin (*TOR*), S6 kinase 1 (*S6K1*) and tumour protein 53 (*TP53*), which are known to extend longevity in mammals. Although the genes do not overlap, growing evidence suggests that downstream molecular processes that are affected in progerias may be important for lifespan extension in mammals. Association studies have linked human longevity to the *INK4a-INK4b* locus, and to polymorphisms in components of the insulin or insulin-like.²¹

DIAGNOSIS

There are no specific tests to diagnose progeria. Identifying the disease often depends on inferences from the physical appearance of the child within the first two years of birth. Genetic testing may also be carried out to detect mutations in the Lamin A gene in a progeria patient.

Recent research has revealed that elevated levels of hyaluronic acid can be detected in the urine of Progeria patients.²²

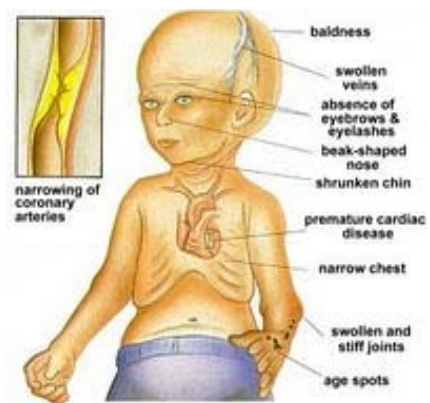


Figure 3: Progeria diagnosis

Low levels of high-density lipoprotein (HDL) cholesterol, also called good cholesterol, that keeps arteries open, can be revealed in a child, through a blood test. This is however not a diagnostic by itself, but will lend support to the diagnosis of Progeria.

Diagnosis can be done based on signs and symptoms, by blood tests revealing, low level of High Density Lipoprotein (HDL), by conducting genetic tests.²³ Stroke or heart attack can be prevented, if the diagnosis is done earlier.



Figure 4: X-Ray of a progeria patient

Making a diagnosis of progeria includes taking a thorough personal and family history, including symptoms, such as poor growth, and completing a physical examination. Failure to thrive and hair loss are the two most basic typical symptoms, which can be used for diagnosis. Testing might be done to help in making a diagnosis of progeria and to assess for the potential for developing atherosclerosis during early childhood, a typical characteristic of progeria. Testing might include a HDL blood test, which can reveal a low level of high-density lipoprotein (HDL) cholesterol, the "good" cholesterol that helps keep arteries open.²⁴

Exams and Tests

The health care provider will perform a physical exam and order laboratory tests. This may show:

- Insulin-resistance
- Skin changes similar to that seen in scleroderma (the connective tissue becomes tough and hardened)

Cardiac stress testing may reveal signs of early atherosclerosis of blood vessels.

Genetic testing can detect changes in the gene that causes progeria.

TREATMENT

There is no cure for progeria. Treatment is aimed at controlling the devastating effects caused by premature aging. Prescribed formulas of antioxidants, vitamins, lipoic acid, and coenzyme-Q are used to increase antioxidant levels. Low antioxidant levels are common in persons with progeria and cause cellular destruction. Research is currently underway to use gene therapy to treat progeria.

Most treatment focuses on reducing complications (such as cardiovascular disease) with heart bypass surgery or low-dose aspirin. Children may also benefit from a high-calorie diet.

Children with Progeria need Physical Therapy (PT) and Occupational Therapy (OT) as often as possible (optimally 2- 3 times each per week) to ensure maximum range of motion and optimal daily functioning throughout their lives.²⁵

Growth hormone treatment has been attempted.

A type of anticancer drug, the farnesyltransferase inhibitors (FTIs), has been proposed, but their use has been mostly limited to animal models. A Phase II clinical trial using the FTI lonafarnib began in May 2007. In studies on the cells another anti-cancer drug, rapamycin, caused removal of progerin from the nuclear membrane through autophagy. It has been proved that pravastatin and zoledronate are effective drugs when it comes to the blocking of farnesyl group production. However, it is important to bear in mind that no treatment is able to cure progeria nowadays.²⁶

- Farnesyltransferase inhibitors (FTIs) are drugs which inhibit the activity of an enzyme needed in order to make a link between progerin proteins and farnesyl groups. This link generates the permanent attachment of the progerin to the nuclear rim.²⁷ In progeria, cellular damage can be appreciated because that attachment takes place and the nucleus is not in a normal state. Lonafarnib is an FTI, which means it can avoid this link, so progerin can not remain attached to the nucleus rim and it has now a more normal state. The delivery of Lonafarnib is not approved by the US Food and Drug Administration (FDA). Therefore, it can only be used in certain clinical trials. Until the treatment of FTIs is implemented in progeria children we will not know its effects -- which are positive in mice.

- Pravastatin is traded as Pravachol or Selektine and it is included in the family of statins. As well as zoledronate (also known as Zometa and Reclast, which is a bisphosphonate), its utility in Hutchinson-Gilford progeria syndrome (HGPS) is the prevention of farnesyl groups formation, which progerin needs to provoke the disease. Some animal trials have been realized using FTIs or a combination of pravastatin and zoledronate so as to observe whether they are capable of reversing abnormal nuclei. The results, obtained by blinded electron microscopic analysis and immunofluorescence microscopy, showed that nucleus abnormalities could be reversed in transgenic mice expressing progerin. The reversion was also observed in vivo -- cultured cells from human subjects with progeria -- due to the action of the pharms, which block protein prenylation (transfer of a farnesyl polypeptide to C-terminal cysteine). The authors of that trial add, when it comes to the results, that: "They further suggest that skin biopsy may be useful to determine if protein farnesylation inhibitors are exerting effects in subjects with HGPS in clinical trials". Unlike FTIs, pravastatin and zoledronate were approved by the U.S. FDA (in 2006 and 2001 respectively), although they are not sold as a treatment for progeria. Pravastatin is used to decrease cholesterol levels and zoledronate to prevent hypercalcaemia.

- Rapamycin, also known as Sirolimus, is a macrolide. There are recent studies concerning rapamycin which conclude that it can minimize the phenotypic effects of progeria fibroblasts. Other observed consequences of its use are: abolishment of nuclear blebbing, degradation of progerin in affected cells and reduction of insoluble

progerin aggregates formation. All these results do not come from any clinical trial, although it is believed that the treatment might benefit HGPS kids.

It should always be taken in account that no treatment is delivered in order to cure Hutchinson-Gilford progeria syndrome, for all of them are in pre-clinical stages.

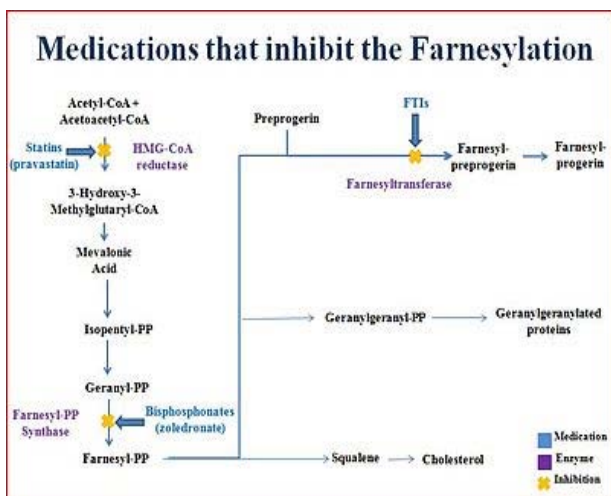


Figure 5: Points where pharms used to inhibit progerin farnesylation act.

PROGNOSIS

As there is no known cure, few people with progeria exceed 13 years of age. At least 90% of patients die from complications of atherosclerosis, such as heart attack or stroke.

Mental development is not adversely affected; in fact, intelligence tends to be above average. With respect to the features of aging that progeria appears to manifest, the development of symptoms is comparable to aging at a rate eight to ten times faster than normal. With respect to features of aging that progeria does not exhibit, patients show no neurodegeneration or cancer predisposition. They also do not develop the so-called "wear and tear" conditions commonly associated with aging, such as cataracts (caused by UV exposure) and osteoarthritis (caused by mechanical wear).

Although there may not be any successful treatments for progeria, there are treatments for the problems it causes, such as arthritic, respiratory, and cardiovascular problems.

EPIDEMIOLOGY

A study from the Netherlands has shown an incidence of 1 in 4 million births. Currently, there are between 35 and 45 known cases in the world. Approximately 100 cases have been formally identified in medical history.

Classical Hutchinson-Gilford Progeria Syndrome is usually caused by a sporadic mutation taking place during the early stages of embryo development. It is almost never passed on from affected parent to child, as affected children rarely live long enough to have children

themselves (very few children with progeria even live past the teen years to be 21).

There have been only two known cases in which it became evident that a healthy person can carry the LMNA mutation that causes progeria. These carriers were identified because they passed it on to their children. One family from India has five children with progeria, although this is not a classical HGPS; they were the subject of a 2005 Bodyshock documentary entitled *The 80 Year Old Children*, while another from Belgium has two.

In September 2011, the first reported case of a black African child with progeria was reported, 12-year-old South African Ontlametse Phalatse. The Progeria Research Foundation at Children's Hospital Boston, affiliated with the Harvard University Medical School, is treating her and monitoring her case.

POPULAR CULTURE

Perhaps one of the earliest influences of progeria on popular culture occurred in the 1922 short story *The Curious Case of Benjamin Button* by F. Scott Fitzgerald (and later released as a feature film in 2008). The main character, Benjamin Button, is born as a seventy-year-old man and ages backwards; it has been suggested that this was inspired by progeria.

In other literary references, Charles Dickens has been suggested in *Bleak House* to have described a case of progeria in the family of Small weed in the grandfather and his grandchildren Judy and twin brother Bart. Orlando Gardiner of the science fiction book series *Otherland* suffers from this disease. The Chuck Palahniuk novel *Haunted* includes one character, Brandon Whittier, who is dying of progeria at 13.

In film, a number of well-known films have featured progeria or progeria-like diseases. The 2009 Bollywood film *Paa*, released in December 2009, has its storyline around progeria (starring Amitabh Bachchan, playing a 13-year old boy Auro). Progeria is also a central theme in the animated film *Renaissance* in which one of the characters finds the much sought cure. The 1996 film *Jack*, starring Robin Williams, portrays a character who has a condition which causes him to age at 4 times the normal rate. This was possibly based on progeria though is otherwise not an accurate portrayal of the syndrome. The 1983 lesbian vampire film, *The Hunger*, starred Susan Sarandon as a physician researching progeria, and showed a vampire (played by David Bowie) undergoing rapid progeria-like aging. In the film *Blade Runner* the character J.F. Sebastian is a genetic designer who is not allowed to emigrate off-world because of his progeria.

The extraterrestrial space traveller in the 1986 film *The Aurora Encounter* was played by Mickey Hays, a teenage boy who suffered from progeria.

In the episode of the series *Dark Angel* titled "Designate This", Max's "younger version" has the disease. Progeria was featured in the *X-Files* episode "Young at Heart,"



where a scientist studying the disease found a way to reverse the aging process.

Rabbi Harold Kushner, author of the well known book, *When Bad Things Happen to Good People*, had a son who suffered from this disease, and his son's illness was probably the impetus for this book on suffering. Leon Botha, a South African visual artist and DJ who appeared in a video for the conceptual rave-rap group Die Antwoord, was one of the oldest people in the world who lived with progeria, dying one day after his 26th birthday on June 5, 2011.²

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