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PROGERIA – A BRIEF 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 laminA 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.

KEY WORDS

Hutchinson-Gilford Progeria Syndrome, premature aging, LMNA, chromosome 1, lamin A, mutation.

INTRODUCTION

Progeria also known as Hutchinson-Gilford Progeria Syndrome (HGPS)[1] is a rare genetic disorder that affects the children and gives them an appearance of accelerated aging. HGPS is caused by a de novo[2] point mutation in the lamin A gene (LMNA) that activates a cryptic splice donor site, producing a truncated mutant protein termed ‘‘progerin’’. Lamin A is a key protein within the nuclear lamina, an intermediate filament meshwork lining the inner nuclear membrane that provides structural support for the nucleus. The word Progeria comes from the Greek “progeros” meaning prematurely old (“pro” means before and “geras” means old age). It is common amongst American children and is highly disseminated in American serials, talk shows and a documentary enacted by affected child artistes.

Use

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Progeria was first described in an academic journal by Dr. Jonathan Hutchinson[3] (1886) and Dr. Hastings Gilford[4] (1897) in England. Thereafter, around 100 cases have been identified so far. It is a rare genetic condition because aging occurs in about one in eight million newborns and most of these affected children hardly survive before they step into adolescent stage. The maximum survival chances are not more than 30 years and the main cause for early death is cardiac failure. The average life expectancy of a child diagnosed with progeria is 13 years, but in some cases children died as early as 7 and some have survived till the age of 30.

HGPS is characterized by retarded growth, partial lipodystrophy, osteoporosis, osteolytic lesions, thin skin, micrognathia, and premature atherosclerosis. The affected children typically look normal at birth and in early infancy, but then grow more slowly than other children and do not gain weight at the expected rate (failure to thrive).

Epidemiology

A study from the Netherlands has shown an incidence of 1 in 4 million births[5]. At present, there are between 35 to 45 known cases in the world.[6] All over the world there are approximately 100 cases have been formally identified in medical history.[7 & 8] It is usually caused by a new (sporadic) mutation during the early division of the cells in the child. It is usually genetically dominant; therefore, parents who are healthy will normally not pass it on to their children[9]. They do not act as carrier. The effected children rarely live long enough to have children themselves. There have been only two known cases in which it became evident that a healthy parent can carry the LMNA mutation that causes progeria. A family from India has five children with progeria[10], they are the subject of a 2005 Body shock documentary entitled *The 80 Year Old Children*. In the other case, a family from Belgium has two children with progeria.[11]

Symptoms

HGPS develops a characteristic facial appearance including prominent eyes, a thin nose with a beaked tip, thin lips, a small chin, and protruding ears. It also causes hair loss (alopecia), aged-looking skin, joint abnormalities, and a loss of fat under the skin (subcutaneous fat). This condition does not disrupt intellectual development or the development of motor skills such as sitting, standing, and walking. Over the course of the disease, the child's heart[12] and circulatory abnormalities become progressively worse and are usually the most significant health problem for children with progeria. These children usually die from cardiovascular problems such as atherosclerosis, but some have died due to convulsions or various types of malnutrition.

The clinical manifestations include the following abnormalities, which are almost always present after age three years:

- **Growth**
  - Short stature and stunted growth
  - Weight distinctly low for height
  - Head disproportionately large for face
- **Body fat**
  - Diminished subcutaneous fat
  - Prominent scalp veins
- **Skin/Teeth**
  - Generalized alopecia
  - Delayed and crowded dentition
- **Skeletal system**
  - Distal phalangeal osteolysis
  - Delayed anterior fontanelle closure
  - Pear-shaped thorax
  - Micrognathia

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- Short, dystrophic clavicles
- "Horse-riding" stance
- Coxa valga
- Thin limbs
- Tightened joint ligaments

- **CVS.** Severe, progressive atherosclerosis with widely variable age of clinical manifestation resulting in myocardial infarction and stroke
- **Other**
  - Prominent eyes
  - Lagophthalmos
  - Wide-based, shuffling gait
  - Failure to complete secondary sexual development

The following features are frequently present:

- **Body fat.** Prominent superficial veins
- **Skin**
  - Thin, taut, dry, wrinkled skin that is brown-spotted in various areas
  - "Sclerodermatous" skin over lower abdomen and proximal thighs, in which irregular bumps reflect underlying lipodystrophy
  - Loss of eyebrows and sometimes eyelashes
  - Dystrophic nails
- **Skeletal system.** Persistently patent anterior fontanel
- **Other**
  - Pinched nose, beaked nasal tip
  - Faint nasolabial cyanosis
  - Thin lips
  - Protruding ears; lack of ear lobes
  - Thin, high-pitched voice

Individuals having most of these features are considered to have the classic Hutchinson-Gilford progeria syndrome. Individuals with either more or less severe feature are considered to have atypical progeria.

Causes

There is a connection between length of telomeres[13] and rapidity of aging. The repeating sequences of TTAGGG that cap each chromosome (known as a telomere) decreases in length after each replication. Once the telomere reaches a critical length the cell can no longer divide, becoming senescent. Progeria patients were found to have excessively short telomeres. Shortening of telomeres is associated with aging skin, blood, muscle, central nervous system, and cardiovascular cells. Progeria patients usually die from heart disease, heart attacks, or stroke around the age of 13. While Progeria patients show abnormal body phenotype, mentally, Progeria patients are normal and can interact with the proper age group[14].

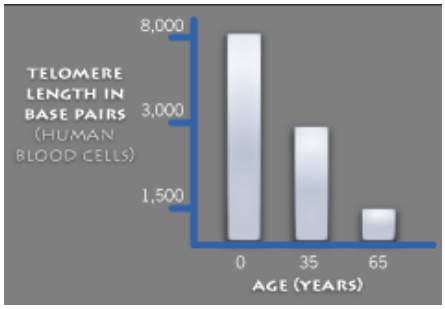

Figure 1.*Telomere length declines in dividing cells as we age (Genetic Science Learning Center, 2004).*

Unlike most other "accelerated aging diseases" progeria is not caused by defective DNA repair. Progeria is an autosomal recessive disease[15]. This means that an individual carrying a mutation in a single gene does not show any sort of symptoms. It has been discovered that ninety percent of the progeria-affected children have a mutation in

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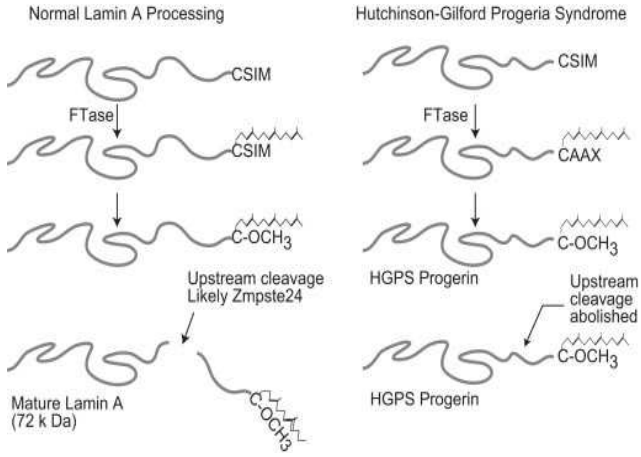
position 1824 of the LMNA gene, replacing cytosine with thymine, creating an unusable form of the protein Lamin A. Lamin A is part of the building blocks of the nuclear envelope. It either develops during cell division in a newly conceived child or in the gametes of one of the parents. However, the real and exact reasons have not yet being identified. Progeria occurs intermittently. It is generally not seen in siblings of affected children. However, in rare cases, it can so happen, that more than one child in a family can succumb to progeria.

Figure 1:

Nuclear lamin A is a protein scaffold on the inner edge of the nucleus that helps organize nuclear processes such as RNA and DNA synthesis. Prelamin A contains a CAAX box at the C-terminus of the protein (where C is a cysteine and A is any aliphatic amino acids). This ensures that the cysteine is farnesylated and allows prelamin A to bind membranes, specifically the nuclear membrane. After prelamin A has been localized to the cell nuclear membrane, the C-terminal amino acids, including the farnesylated cysteine, are cleaved off by a specific protease. The resulting protein is now lamin A, is no longer membrane-bound, and carries out functions inside the nucleus.



In HGPS, the recognition site that the enzyme requires for cleavage of prelamin A to lamin A is mutated. Lamin A cannot be produced, and prelamin A builds up on the nuclear membrane, causing a characteristic nuclear blebbing[16]. This results in the premature aging symptoms of progeria, although the mechanism connecting the misshapen nucleus to the symptoms is not known.

A study that compared HGPS patient cells with the skin cells from LMNA young and elderly human subjects found similar defects in the HGPS and elderly cells, including down-regulation of certain nuclear proteins, increased DNA damage, and demethylation of histone, leading to reduced heterochromatin[17]. Nematodes over their lifespan show progressive lamin changes comparable to HGPS in all cells but neurons and gametes[18]. These studies suggest that lamin A defects contribute to normal aging.

LMNA gene

The official name of this gene is “lamin A/C.”
LMNA is the gene's official symbol. The LMNA gene is also known by other names, listed below.

- LMN1

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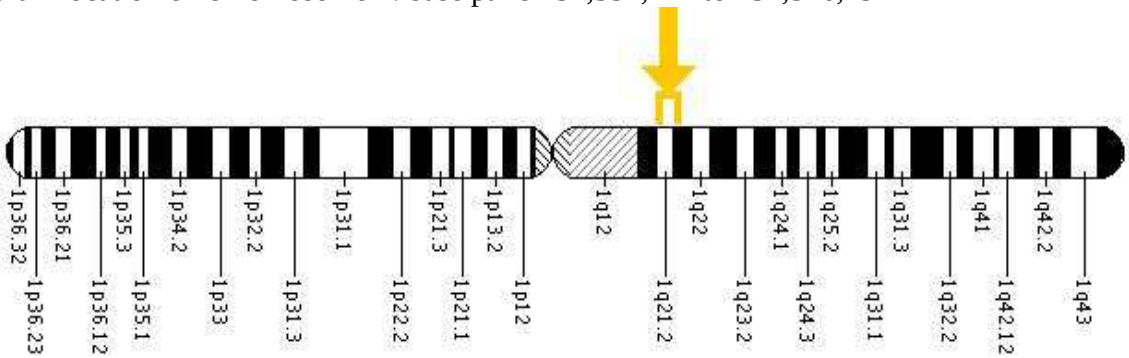
- LMNA_HUMAN
- LMNC

The LMNA gene location

Cytogenetic Location: 1q21.2-q21.3
Molecular Location on chromosome 1: base pairs 154,351,121 to 154,376,494



The LMNA gene is located on the long (q) arm of chromosome 1 between positions 21.2 and 21.3. More precisely, the LMNA gene is located from base pair 154,351,121 to base pair 154,376,494 on chromosome 1.

Chromosome 1

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 1, one copy inherited from each parent, form one of the pairs. Chromosome 1 is the largest human chromosome, spanning about 247 million base pairs (the building blocks of DNA) and representing approximately 8 percent of the total DNA in cells. Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 1 likely contains more than 3,000 genes. These genes perform a variety of different roles in the body. Genes on chromosome 1 are among the estimated 20,000 to 25,000 total genes in the human genome.

Changes in chromosome 1 related to health conditions

Many genetic conditions are related to changes in particular genes on chromosome 1. This list of disorders associated with genes on chromosome 1 provides links to additional information. Changes in the structure or number of copies of a chromosome can also cause problems with health and development. The following chromosomal conditions are associated with such changes in chromosome1.

Cancers

Changes in the structure of chromosome 1 are associated with certain forms of cancer and conditions related to cancer. These changes are typically somatic, which means they are acquired during a person's lifetime and are present only in

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tumor cells. Deletions in the short (p) arm of the chromosome have been identified in tumors of the brain and kidney. Duplications in the long (q) arm of the chromosome have been reported in a disorder called myelodysplastic syndrome, which is a disease of the blood and bone marrow. People with this condition have a low number of red blood cells (anemia) and an increased risk of developing leukemia.

1p36 deletion syndrome

1p36 deletion syndrome is caused by a deletion of genetic material from a specific region in the short (p) arm of chromosome 1. The signs and symptoms of this disorder, which include intellectual disability, distinctive facial features, and structural abnormalities in several body systems, are probably related to the loss of multiple genes in this region. The size of the deletion varies among affected individuals.

Thrombocytopenia-absent radius syndrome

Everyone diagnosed with thrombocytopenia-absent radius (TAR) syndrome, which is characterized by bleeding problems and abnormal development of the forearms, has had a deletion of genetic material on chromosome 1. The deletion removes about 200,000 DNA building blocks (200 kilo bases, or 200 kb) from the long (q) arm of the chromosome at position 1q21.1. This section of the chromosome contains 11 genes. The loss of multiple genes in this region is believed to be responsible for TAR syndrome. Not all people who inherit the deletion of genetic material on chromosome 1 associated with TAR syndrome will develop the disorder. Even within a single family, some people with the deletion may have TAR syndrome while others are unaffected. For this reason, researchers believe that the 1q21.1 200 kb deletion is needed to cause TAR syndrome but that some other, unknown genetic change must also be present.

Other chromosomal conditions

Other changes in the number or structure of chromosome 1 can have a variety of effects, including delayed growth and development, distinctive facial features, birth defects, and other medical problems. Changes to chromosome 1 may include an extra segment of the short (p) or long (q) arm of the chromosome in each cell (partial trisomy 1p or 1q), a missing segment of the short or long arm of the chromosome in each cell (partial monosomy 1p or 1q), or a circular structure called ring chromosome 1. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

The normal function of the LMNA gene

The LMNA gene provides instructions for making several slightly different proteins called lamins. The two major proteins produced from this gene, lamin A and lamin C, are made in most of the body's cells. These proteins have a nearly identical sequence of protein building blocks (amino acids). The small difference in the sequence makes lamin A longer than lamin C.

Lamins A and C are structural proteins called intermediate filament proteins. Intermediate filaments provide stability and strength to cells. Lamins A and C are essential scaffolding (supporting) components of the nuclear envelope, which is a structure that surrounds the nucleus in cells. Specifically, these proteins are located in the nuclear lamina, a mesh-like layer of intermediate filaments that is attached to the inner membrane of

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the nuclear envelope. The nuclear envelope regulates the movement of molecules into and out of the nucleus, and researchers believe it may play a role in regulating the activity of certain genes.

The lamin A protein must be processed within the cell before becoming part of the lamina. Its initial form, called prelamin A, undergoes a complex series of steps that are necessary for the protein to be inserted into the lamina. Lamin C does not have to undergo this processing before becoming part of the lamina.

Changes in the LMNA gene related to health conditions

Charcot-Marie-Tooth disease: It is caused by mutation in the LMNA gene

At least one LMNA mutation has been identified in people with a form of Charcot-Marie-Tooth disease known as type 2B1. The mutation changes a single amino acid in the LMNA proteins. Specifically, the amino acid arginine is replaced by the amino acid cysteine at protein position 298 (written as Arg298Cys or R298C). Although its effect is not fully understood, the Arg298Cys mutation alters a protein region important for interactions with other molecules. It is unclear how the altered LMNA proteins contribute to the signs and symptoms of type 2B1 Charcot-Marie-Tooth disease.

Emery-Dreifuss muscular dystrophy - caused by mutations in the LMNA gene

More than 100 mutations in the LMNA gene have been identified in people with Emery-Dreifuss muscular dystrophy. Most of these mutations change single amino acids in lamins A and C, which alters the structure of these proteins. The effect of LMNA mutations within cells remains unclear. Abnormal versions of lamins A and C may alter the activity of certain genes or weaken the structure of the nucleus, making cells more fragile. Researchers continue to investigate how LMNA mutations affect muscles used for movement (skeletal muscles) and heart (cardiac) muscle, leading to the characteristic features of Emery-Dreifuss muscular dystrophy.

Hutchinson-Gilford progeria syndrome - caused by mutations in the LMNA gene

A specific mutation in the LMNA gene has been found in most patients with Hutchinson-Gilford progeria syndrome. This mutation changes a single DNA building block (nucleotide) in the gene. Specifically, the mutation replaces the nucleotide cytosine with the nucleotide thymine at position 1824 (written as C1824T). This mutation is also sometimes noted as Gly608Gly or G608G, which refers to the position in the lamin A protein affected by the mutation. The C1824T mutation leads to an abnormal version of the lamin A protein called progerin, which is missing 50 amino acids near one end. The location of this mutation does not affect the production of lamin C. Other mutations in the LMNA gene have been identified in a small number of people with the features of Hutchinson-Gilford progeria syndrome.

The mutations responsible for this disorder result in an abnormal version of lamin A that cannot be processed correctly within the cell. When the altered protein is incorporated into the lamina, it can disrupt the shape of the nuclear envelope. Over time, a buildup of this altered protein appears to damage the structure and function of the nucleus, making cells more likely to die prematurely. Researchers are working to determine how these changes lead to the signs and symptoms of Hutchinson-Gilford progeria syndrome.

Other disorders - caused by mutations in the LMNA gene

Mutations in the LMNA gene have been found to cause several other inherited conditions. Because the

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conditions result from mutations in lamin proteins, they are known as laminopathies. A laminopathy[19] called limb-girdle muscular dystrophy type 1B affects skeletal and cardiac muscle. Another condition, familial dilated cardiomyopathy with conduction defects, has severe effects on cardiac muscle that result in life-threatening heart problems. The features of these laminopathies overlap with those of the autosomal dominant form of Emery-Dreifuss muscular dystrophy. Because certain LMNA mutations may be responsible for any of these conditions, researchers suspect that limb-girdle muscular dystrophy type 1B and familial dilated cardiomyopathy with conduction defects may be variants of Emery-Dreifuss muscular dystrophy instead of separate disorders.

Other laminopathies affect the amount and distribution of fat in the body. Dunnigan type partial lipodystrophy is characterized by a loss of fatty tissue from the trunk and limbs, and a buildup of fat around the neck and shoulders. Mandibuloacral dysplasia also alters the distribution of fatty tissue and causes abnormalities in some bones, particularly in the jaw, hands, and feet.

Researchers have not determined how mutations in the LMNA gene result in this diverse group of disorders. They believe that altered lamin proteins could disrupt the activity of genes in specific tissues. Altered lamins may also weaken the structure of the nucleus in some cells, making them more fragile.

Clinical Diagnosis

Actually there is no clinically approved test for diagnose progeria up to date. Until 2003, In order to diagnose Progeria, doctors observed phenotype i.e. physical symptoms, such as skin changes and a failure to gain weight, which were not fully apparent until a child's first or second year of life, as well as x-rays of patients and Urinary hyaluronic acid testing but had no definitive test.

Urinary hyaluronic acid testing: Chemical tests may reveal elevated levels of chemical hyaluronic acid in the urine as well as certain fatty compounds, and reduced levels of certain primary antioxidant enzymes in the blood. This may also increase likelihood of death, as one cause of aging is believed to be a build up of oxidants in the blood over time (Progeria Project Foundation, 2002).Although urinary hyaluronic acid has been reported to be increased in most children with HGPS[20] the measurement is now regarded as unreliable[21] and is not recommended for diagnosis.

Now- a-days, with the discovery of the mutated Lamin A gene, blood samples and a skin biopsy taken from patients can be evaluated for presence of the mutated gene. This gives a definitive diagnosis (Progeria Research Foundation, 2003). Additionally, the Progeria Research Foundation has set up a new Diagnostic Program whose first goal is to establish a Progeria cell and tissue bank to assist in further research. Scientists are exploring possibilities of using existing drugs to block or reduce production of the abnormal Lamin A protein in children with Progeria. Screening technologies could also be used to reverse nuclear membrane abnormalities in Progeria children's cells (National Human Genome Research Institute, 2003). Today the only treatment for Progeria patients is administering a low dose of aspirin21 throughout their lives. Aspirin may help prevent atherothrombotic events, stroke and heart attacks by hindering platelet aggregation. Currently there is no cure for the disease (Progeria Research Foundation, 2003).

Prenatal Testing: Prenatal diagnosis for HGPS is possible by analysis of DNA extracted from fetal

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cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: (1) Because HGPS has thus far not been reported to recur in families, prenatal testing would only be performed because of the (unlikely) possibility of germline mosaicism in one of the parents.

(2) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Pre implantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member for laboratories offering PGD.

Note: Because HGPS has thus far not been reported to recur in families, PGD would only be performed because of the (unlikely) possibility of germline mosaicism in one of the parents.

Hutchinson-Gilford progeria syndrome inheritation process

Hutchinson-Gilford progeria syndrome is considered an autosomal dominant condition, which means one copy of the altered gene in each cell is sufficient to cause the disorder. The condition results from new mutations in the LMNA gene, and almost always occurs in people with no history of the disorder in their family. A 2003 report in Nature[22] said that progeria may be a de novo dominant trait. It develops during cell division in a newly conceived zygote or in the gametes of one of the parents. It is caused by mutations in the LMNA (lamin A protein) gene on chromosome 1; the mutated form of lamin A is commonly known as progerin. One of the authors, Leslie Gordon, was a physician who didn't know anything about progeria until her own son, Sam, was diagnosed at 21 months. Gordon and her husband, pediatrician Scott Berns, founded the Progeria Research Foundation[23].

Risk to Family Members

Parents of a proband:

- All probands with HGPS have the disorder as the result of a *de novo* mutation.
- Parents of probands are not affected.

Sibs of a proband:

- The risk to the sibs of a proband is small.
- One instance of apparent somatic and germline mosaicism has been reported[24]. Therefore, the recurrence risk may be on the order of one in 500, as in other *de novo* dominant mutations.
- With the exception of two sets of identical twins with HGPS, the authors are unaware of any convincing cases of a family with more than one sib with classic HGPS.

Offspring's of a proband**:** Individuals with HGPS do not reproduce.

Other family members of a proband**:** Because HGPS occurs as the result of a *de novo* mutation, other family members of a proband are not at increased risk.

Related Genetic Counseling Issues

Origin of *de novo* mutation: As with *de novo* mutations in achondroplasia, all informative *LMNA* mutations have been paternal in origin, though the number of families evaluated is small[3]. A paternal age effect is present as the father's age is significantly increased by about five years on average. There is no increase in consanguinity.

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Treatment

There is no particular treatment for the progeria, and research is going on to treat the condition. Following precautions and indications may improve the condition.

Medications: Dosages should be based on body weight or body surface area and not on age. Anesthetics should be used with particular caution.
Nitroglycerin is frequently of benefit if angina develops.
Routine anticongestive therapy is appropriate if congestive heart failure (CHF) is present.
Injuries: Children are susceptible to fractures; treatment is routine.
Hips: Children are particularly susceptible to hip dislocation because of the coxa valga malformation.
Conservative management with physical therapy and body bracing and avoidance of surgical procedures on bones are recommended when possible.
Teeth: Delayed loss of primary teeth is common. Extractions may be required to avoid crowding and development of two rows of teeth.
Physical therapy: Routine physical and occupational therapy is recommended to help maintain range of motion in large and small (i.e., finger) joints. Active stretching and strengthening, along with hydrotherapy, are recommended.
Prevention of Primary Manifestations
Aspirin: Based on the evidence from adult studies that low doses of aspirin help delay heart attacks and strokes, it is probably appropriate to give children with HGPS one "baby" aspirin every other day. If chicken pox or influenza is prevalent in the community, it may be advisable to discontinue the aspirin during that time because of the increased risk of Reye syndrome. Stronger anticoagulation is appropriate if vascular blockage, transient ischemic attacks (TIAs), stroke, angina or myocardial infarction are detected.
Vitamin supplementation: Standard amounts of ordinary multiple vitamin tablets are appropriate.
Fluoride supplements are recommended in areas where needed.
Immunizations: The routine doses and administration schedule for DPT, MMR, and polio immunizations are recommended. Conjugated hemophilus influenza vaccine for children ages 18 months through five years is recommended.
Surveillance
ECG, echocardiogram, and carotid duplex scans annually or semi-annually to monitor for cardiovascular disease (Children may experience severe carotid artery atherosclerotic blockage prior to any significant ECG changes.)
Yearly lipid profiles
Yearly dental examination and x-ray
Physical and occupational therapy multiple times per week
Hip x-rays every few years to evaluate for avascular necrosis and progressing coxa valga
Agents/Circumstances to Avoid
Children should avoid being in the midst of large crowds with much taller and larger peers because of the increased risk of injury.

Drugs under clinical trails

A Study of Zoledronic Acid, Pravastatin, and Lonafarnib for Patients with Progeria
This study is ongoing, but not recruiting participants.

Sponsor	Children's Hospital Boston
Collaborators	Dana-Farber Cancer Institute Brigham and Women's Hospital Schering-Plough

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Information provided by	Children's Hospital Boston
ClinicalTrials.gov Identifier	NCT00879034

Purpose

Progeria is a rare "premature aging" disease in which children dies of severe atherosclerosis leading to strokes and heart attack. It is a multisystem disease with objective clinical markers for disease progression. These include abnormalities in growth and body composition, bone mineral density, and join function, endocrine function, alopecia, and vascular disease. There is currently no therapy proven effective for any of the progressive and deleterious aspects of this disorder.

Progeria is caused by a gene defect in the gene LMNA, coding for the nuclear protein lamin A. Lamin A is normally expressed by most differentiated cells, and requires posttranslational farnesylation[25] to incorporate into the nuclear membrane. This trial proposes to use three agents (zoledronic acid, pravastatin, and lonafarnib) to inhibit farnesylation of abnormal lamin, the disease causing protein in Progeria. The primary objective of this study is to evaluate the feasibility of administering intravenous zoledronic acid, oral pravastatin and oral lonafarnib, to patients with Progeria for a minimum of 4 weeks.

Condition	Intervention	Phase
Progeria	Drug: Lonafarnib Drug: Zoledronic Acid Drug: Pravastatin	Phase II

Study Type: Interventional

Study Design: Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety Study.

Official Title: A Phase II Pilot Study of Zoledronic Acid, Pravastatin, and Lonafarnib (SCH66336) for Patients With Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies

Further study details as provided by Children's Hospital Boston

Primary Outcome Measures:

- The primary objective of this study is to evaluate the feasibility of administering intravenous zoledronic acid, oral pravastatin and oral lonafarnib, to patients with Progeria for a minimum of 4 weeks

Secondary Outcome Measures:

- To describe any acute and chronic toxicities associated with treating progeria patients with the combination of zoledronic acid, pravastatin and lonafarnib
- To investigate which clinical and laboratory studies are needed to monitor or alter therapy to prevent unacceptable toxicity.
- To assess the pharmacokinetics of lonafarnib in patients with progeria.
- To assay for the inhibition of HDJ-2 farnesylation in Peripheral Blood Leukocytes (PBL)
- To obtain baseline clinical and laboratory data so that longer-term measures of efficacy will be *achievable if treatment continues beyond the 4-week feasibility study period.*

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Intervention Details

Drug: Lonafarnib

Lonafarnib capsules are to be orally administered twice per day approximately every 12 hours. Lonafarnib dosing will begin at 150 mg/m2 by mouth twice daily. Dose levels are 150, 115, 90 and 70 mg/m2. Patients experiencing significant drug related grade 3 or 4 toxicity and not responding to therapy interruption or supportive care measures will be dose reduced by one dose level.

Drug: Zoledronic Acid

Zoledronic acid will be administered intravenously at week one of this treatment trial. Week one administration will consist of one infusion over a 30 minute period, 0.0125 mg/kg body weight.

Drug: Pravastatin

Pravastatin will begin at 5 mg by mouth once daily for children weighing less than 10 kg, and 10 mg by mouth once daily for children weighing 10 kg or greater.

Detailed Description:

This is an open label single arm feasibility trial. A combination of two oral agents (pravastatin and lonafarnib) and one intravenous (IV) agent (zoledronic acid) will be administered at doses and schedule currently applied in pediatrics. These agents all target farnesylation pathways at different points. Our goal is to inhibit farnesylation of abnormal lamin, the disease-causing protein in Hutchinson-Gilford Progeria Syndrome and progeroid laminopathies (henceforth "progeria"). The drugs will include the intravenous bisphosphonate zoledronic acid, oral HMG co-reductase inhibitor pravastatin and the oral farnesyltransferase inhibitor (FTI) lonafarnib (SCH 66336). Patients with genetically confirmed progeria will be eligible for this protocol. Treatment will be initiated for 4 weeks duration and may be extended depending on tolerability. This study will assess the feasibility of this treatment regimen in the first 4 weeks. If tolerated for 4 weeks, patients can be treated with this regimen for up to 6 months.

Eligibility

Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Genetic Diagnosis: All patients must have confirmatory mutational analysis showing mutation in the lamin A gene.
- Patients must display clinical signs of progeria as per the clinical trial team.
- Patients must be willing and able to come to Boston for appropriate studies and examinations at initiation of study and at week 4 of study.
- Patient must have adequate organ and marrow function as defined by study parameters

Exclusion Criteria:

- Other than the drugs used in this protocol, other drugs targeted to treat Progeria are excluded. Drugs to treat symptoms of Progeria are permitted.
- Patients must not be taking medications that significantly affect the metabolism of lonafarnib at the time they start lonafarnib.
- Patient must have no uncontrolled infection.
- Subjects who have known or suspected hypersensitivity to any of the excipients included in the formulation should not be treated.
- Patients must not be pregnancy of breast-feeding. Female patients of childbearing potential must have negative serum or urine pregnancy test. Male and female patients of reproductive potential must agree to use a medically accepted form of birth control while on study and up to 10 weeks after treatment. It is permissible for female patients to take oral contraceptives or other hormonal methods while receiving treatment with lonafarnib.

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Other premature aging syndromes

The following are other syndromes that include some features of premature aging:

- Neonatal progeroid syndrome[26] (Weidemann-Rautenstrauch syndrome)
- Acrogeria[27]
- Cockayne syndrome[22](Weber-Cockayne syndrome, or Neill-Dingwall Syndrome)
- Hallermann-Streif syndrome[28] (François Dyscephalic Syndrome, Hallermann-Streiff-François syndrome, Oculomandibulodyscephaly with hypotrichosis and Oculomandibulofacial syndrome)
- Gerodermia osteodysplastica[29] (geroderma osteodysplasticum and Walt Disney dwarfism)
- Berardinelli-Seip congenital lipodystrophy[30] (congenital generalized lipodystrophy)
- Petty-Laxova-Weidemann progeroid syndrome
- Ehlers-Danlos syndrome, progeroid form[31]
- Werner syndrome[23 & 32]

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