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Hutchinson-Gilford Progeria Syndrome

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Summary

Clinical characteristics.

Hutchinson-Gilford progeria syndrome encompasses a spectrum of clinical features that typically develop in childhood and resemble some features of accelerated aging. Although signs and symptoms vary in age of onset and severity, they are remarkably consistent overall. Children with Hutchinson-Gilford progeria syndrome (HGPS) usually appear normal at birth. Profound failure to thrive occurs during the first year. Characteristic facies, with receding mandible, narrow nasal bridge and pointed nasal tip develop. During the first to third year the following usually become apparent: partial alopecia progressing to total alopecia, loss of subcutaneous fat, progressive joint contractures, bone changes, nail dystrophy, and abnormal tightness and/or small soft outpouchings of the skin over the abdomen and upper thighs, and delayed primary tooth eruption. Later findings include low-frequency conductive hearing loss, dental crowding, and partial lack of secondary tooth eruption. Additional findings present in some but not all affected individuals include photophobia, excessive ocular tearing, exposure keratitis,

and Raynaud phenomenon. Motor and mental development is normal. Death occurs as a result of complications of severe atherosclerosis, either cardiac disease (myocardial infarction) or cerebrovascular disease (stroke), generally between ages six and 20 years. Average life span is approximately 14.6 years.

Diagnosis/testing.

The diagnosis is based on recognition of common clinical features and detection of heterozygous *LMNA* pathogenic variants either within exon 11 (termed classic HGPS) or at the intronic border of exon 11 (termed atypical HGPS). *LMNA* is the only gene in which pathogenic variants are known to cause HGPS.

Management.

Treatment of manifestations: A regular diet with frequent small meals is recommended. Treatment for an abnormal lipid profile includes exercise as cardiovascular and neurologic status allow, diet modification, and medication such as statins as warranted. Routine physical and occupational therapy, active stretching and strengthening exercises, and hydrotherapy are recommended. Medication dosages are based on body weight or body surface area, not age. General anesthesia and intubation should be performed with extreme caution, ideally with fiberoptic intubation, if possible. Anticongestive therapy is routine for the treatment of congestive heart failure. Exposure keratopathy caused primarily by nocturnal lagophthalmos can be treated with ocular lubrication. Hearing aids can be used, when clinically necessary. Hip dislocation is best managed with physical therapy and body bracing; surgery involving bones should be avoided if possible. Primary tooth extractions may be required to avoid dental crowding. Shoe pads are recommended, as lack of body fat leads to foot discomfort. Use of sunscreen on all exposed areas of skin, including the head, is recommended for outdoor activities. Age-appropriate schooling is usually recommended.

Prevention of secondary complications: Low-dose aspirin (2-3 mg/kg body weight) is recommended for prevention of cardiovascular and stroke complications. Because the stiffened peripheral vasculature may be less tolerant to dehydration, maintaining optimal hydration orally is recommended.

Surveillance: Annual or semi-annual electrocardiogram (ECG), annual echocardiogram, carotid duplex ultrasound examination, neurologic examination, MRI/MRA of the head and neck, lipid profile, dental examination, audiometry, ophthalmology examination, dual x-ray absorptiometry and/or peripheral cutaneous computed tomography to measure bone density, hip x-ray to evaluate for avascular necrosis and progressing coxa valga, assessment for joint contractures, and assessment of activities of daily living.

Agents/circumstances to avoid: Dehydration; large crowds with taller/larger peers because of the risk of injury. Physical activity should be self-limited.

Genetic counseling.

Almost all individuals with HGPS have the disorder as the result of a *de novo* autosomal dominant pathogenic variant. Because HGPS is typically caused by a *de novo* pathogenic variant, the risk to the sibs of a proband is small. However, one instance of apparent somatic and germline mosaicism in a parent has been reported; thus, the recurrence risk for parents of a child with HGPS may be on the order of one in 500. Because of the (unlikely) possibility of recurrence as a result of germline mosaicism in one of the parents, prenatal testing is possible.

GeneReview Scope

Hutchinson-Gilford Progeria Syndrome: Included Phenotypes

- Hutchinson-Gilford progeria syndrome (HGPS), classic
- Atypical Hutchinson-Gilford progeria syndrome

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical Diagnosis

The diagnosis of a Hutchinson-Gilford progeria syndrome (HGPS) should be considered in individuals who have the following features:

- **Growth**
  - Short stature (<3rd percentile), lifelong
  - Weight (<3rd percentile), lifelong
  - Weight distinctly low for height
  - Head disproportionately large for face
  - Thin, high-pitched voice
- **Body fat.** Diminished subcutaneous fat globally, with the following sequellae:
  - Prominent scalp veins
  - Prominent veins over most of body
  - Circumoral cyanosis
  - Prominent eyes
  - Lack of ear lobes in some not all) cases
- **Skin/hair/nails/eyes**
  - Taut, dry skin that is variably pigmented (spotty)
  - "Sclerodermatous" skin over lower abdomen and proximal thighs
  - Irregular small outpouchings of skin over lower abdomen and/or proximal thighs
  - Generalized alopecia with sparse downy hairs on the occiput
  - Loss of eyebrows and sometimes eyelashes
  - Dystrophic fingernails and toenails
  - Nocturnal lagophthalmos (the inability to fully close the eye) and, in a minority of cases, corneal ulceration due to exposure keratitis
  - Thin lips
- **Audiologic.** Low-frequency conductive hearing loss
- **Oral/dental**
  - Delayed eruption of primary teeth
  - Delayed loss of erupted primary teeth

    - Partial secondary tooth eruption
    - Dental crowding as a result of small mouth, lack of primary tooth loss, and secondary tooth eruption behind primary teeth
    - Ogival (steeple-shaped) palatal vault (60%-70% of affected individuals)
    - Short, thick lingual frenum that limits tongue mobility (50% of affected individuals)
- **Skeletal system/joints**
    - Narrow nasal bridge, pointed nasal tip
    - Osteolysis of the distal phalanges
    - Delayed closure of the anterior fontanelle
    - Pear-shaped thorax
    - Retrognathia and micrognathia
    - Short, dystrophic clavicles
    - Osteoarthritis
    - "Horse-riding" stance and wide-based, shuffling gait
    - Coxa valga
    - Low bone density
    - Thin limbs
    - Tightened joint ligaments globally but variable in severity
- **Cardiovascular/neurovascular**
    - Severe progressive atherosclerosis with variable age of clinical manifestation resulting in:
        - Cardiac manifestations: angina, congestive heart failure, myocardial infarction
        - Stroke, including clinical strokes, transient ischemic attacks, and silent strokes that are seen on MRI or CT of the head but do not manifest as clinical deficits
    - Raynaud phenomenon in fingers in a minority of affected individuals
- **Endocrine**
    - Failure to complete secondary sexual development
    - Low serum leptin concentration
    - Insulin resistance in up to 50% of individuals. Note that frank diabetes mellitus is unusual.

Establishing the Diagnosis

The diagnosis of **classic Hutchinson-Gilford progeria syndrome** is based on recognition of common clinical features listed above and detection of the c.1824C>T (p.Gly608Gly) heterozygous *LMNA* pathogenic variant.

The diagnosis of **atypical Hutchinson-Gilford progeria syndrome (HGPS)** is made in individuals with clinical features similar to classic HGPS who have progerin-producing pathogenic variants in intron 11 of *LMNA* (see Table 1 and Table 4).

Table 1.

Classic HGPS and Atypical HGPS: Causative Allelic Variants and Comparative Clinical Phenotypes

Phenotype	Causative Variants in *LMNA*	Clinical Features Compared to HGPS	# of Affected Persons Identified	Reference
Classic HGPS	c.1824C>T	NA	NA	Eriksson et al [2003], De Sandre-Giovannoli & Lévy [2006], Merideth et al [2008]
Atypical HGPS	c.1822G>A	Slightly more severe	4	PRF
	c.1968+1G>A	Slightly to moderately more severe	4	Moulson et al [2007], PRF
	c.1968+2T>A	Similar	2	PRF
	c.1968+2T>C	Similar	1	PRF
	c.1968+5G>C	Similar	3	PRF

HGPS = Hutchinson-Gilford progeria

PRF = Progeria Research Foundation Diagnostic Testing Program

NA = not applicable

Molecular Genetic Testing

Gene. *LMNA* is the only gene in which mutation is known to cause HGPS.

- **Classic HGPS.** c.1824C>T transition in exon 11 results in a silent Gly-to-Gly change at codon 608 (p.Gly608Gly). This silent change results in increased usage of an internal cryptic splice site resulting in an in-frame deletion of 150 nucleotides and 50 amino acids from the lamin A protein.
- **Atypical HGPS.** c.1822G>A (p.Gly608Ser), c.1968+1G>A, c.1968+2T>A, c.1968+2T>C, and c.1968+5G>C pathogenic variants in *LMNA* result in progerin production and clinical phenotypes similar to classic HGPS.

Clinical testing

Table 2.

Summary of Molecular Genetic Testing Used in Hutchinson-Gilford Progeria Syndrome

Gene [1]	Test Method	Allelic Variants Detected [2]	Variant Detection Frequency
LMNA	Targeted analysis for pathogenic variants	c.1824C>T	100% [3]
	Sequence analysis [4] of the coding and flanking intronic regions	Sequence variants throughout the gene	See footnote 5

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Classic Hutchinson-Gilford progeria syndrome (HGPS, progeria) is defined by the presence of *LMNA* variant c.1824C>T [Cao & Hegele 2003, De Sandre-Giovannoli et al 2003, Eriksson et al 2003].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Detects the common c.1824C>T variant for classic HGPS, variants that define atypical HGPS (c.1822G>A, c.1968+1G>A, c.1968+2 T>A, c.1968+2T>C, and c.1968+5G>C) and other sequence variants that lead to related phenotypes (see Genetically Related Disorders, Table 1, and Table 4).

Testing Strategy

To confirm/establish the diagnosis in a proband

- Establish the clinical diagnosis based on age-related findings (see Clinical Diagnosis).
- Molecular genetic testing of *LMNA* using EITHER of the following confirms the diagnosis:
  - Targeted analysis for the pathogenic variant associated with classic HGPS
  - Sequence analysis of the entire coding region and associated splice junctions to identify the one pathogenic variant associated with classic HGPS and the pathogenic variants associated with atypical HGPS (see Table 2)

Clinical Characteristics

Clinical Description

Classic Hutchinson-Gilford progeria syndrome (HGPS) is characterized by clinical features that develop in childhood and resemble some features of accelerated aging.

Children with progeria usually appear normal at birth and in early infancy. Early findings such as midfacial cyanosis, "sculpted nose," and "sclerema" (or "sclerodermatous skin") may suggest HGPS at or shortly after birth. Profound failure to thrive usually occurs during the first year. Characteristic facies, partial alopecia progressing to total alopecia, loss of subcutaneous fat, stiffness of joints, bone changes, and abnormal tightness of the skin over the abdomen and upper thighs usually become apparent during the second to third year.

Children are particularly susceptible to hip dislocation because of the progressive coxa valga malformation.

Delayed loss of primary teeth is common.

Motor and mental development is normal.

As a result of severe failure to thrive, affected individuals do not become sexually mature and do not reproduce.

Insulin resistance occurs about 50% of the time, without overt development of diabetes mellitus.

Tumor rate is not increased over that of the general population. One individual died of a chondrosarcoma of the chest wall at age 13 years [King et al 1978].

Other changes associated with normal aging such as near-sightedness or far-sightedness, arcus senilis, senile personality changes, or Alzheimer disease have not been documented. Children with HGPS appear to have a normal immune system; they respond as well as the general population when subjected to various infections. Wound healing is normal.

Individuals with HGPS develop severe atherosclerosis, usually without obvious abnormalities in lipid profiles [Gordon et al 2005]. In general, serum cholesterol and triglyceride concentrations are not elevated and HDL concentrations may decrease with age. Early cardiac changes can manifest in years five through eight, but usually begin to occur after age eight years. Typical manifestations of cardiovascular decline include heart valve and chamber decline as a result of increased afterload, angina, and late findings including dyspnea on exertion. Hypertension is usually a later sign of vascular disease.

Transient ischemic attacks, silent strokes, or symptomatic strokes have occurred as early as age four years [Silvera et al 2013]. Strokes can occur at any brain site and, therefore, can lead to a variety of physical limitations and/or cognitive decline. Partial and complete carotid artery blockages can occur from plaque formation. Despite underlying vascular disease some children do not have clinically identified strokes.

Death occurs as a result of complications of cardiac or cerebrovascular disease (heart attack or stroke) generally between ages six and 20 years, with an average life span of approximately 14.6 years [Gordon et al 2014].

Atypical HGPS is characterized by similar but sometimes subtly more or less severe clinical features compared to individuals with HGPS.

- One living child with c.1968+2T>A displayed HGPS clinical characteristics with the exception that lower trunk and upper and lower leg skin findings were more severe than usually seen in classic HGPS.
- One living child with c.1968+2T>C displayed a slightly milder form of HGPS, with more hair than usual, but still extremely sparse, wispy immature hair phenotype.
- In two children with c.1968+5G>C the phenotype was clinically indistinguishable from HGPS. One is living and the other died at age 12.6 years. Cause of death was intraoperative complications during corrective hip surgery.
- In one child with c.1968+1G>C the phenotype was clinically more severe than HGPS. She had a stroke at age three years, had multiple episodes of pneumonia, and died at age 5.8 years of respiratory distress.

Genotype-Phenotype Correlations

See Table 1 and Clinical Description.

- Individuals with the HGPS-causing common c.1824C>T variant appear remarkably similar in phenotype [Eriksson et al 2003].
- The child with the c.1822G>A pathogenic variant and a more severe progeroid laminopathy had more growth retardation and subcutaneous calcification on the hands, and died at age eight years.
- The child with the c.1968+1G>A pathogenic variant and a more severe progeroid laminopathy had more growth retardation and tighter skin, and died at age 3.5 years during an episode of gastroenteritis and pneumonia [Moulson et al 2007].

Penetrance

Penetrance is complete.

Nomenclature

First reported by Hutchinson [1886] and later by Gilford [1904], HGPS is also referred to as the Hutchinson-Gilford syndrome, progeria, or progeria of childhood.

Prevalence

The proportion of children with HGPS per total population is one in eighteen million [Gordon et al 2014].

The estimated birth incidence for HGPS is one in four million births with no observed differences based on ethnic background [Hennekam 2006].

Genetically Related (Allelic) Disorders

More than ten other diseases and conditions with pathogenic variants or variations in *LMNA* have been identified. See OMIM 150330.

Progeroid-producing progeroid laminopathy or "progeroid laminopathy" can be used to describe phenotypes that have overlap with but are obviously different from HGPS. Various pathogenic variants in *LMNA* (identified through the Progeria Research Foundation Diagnostic Testing Program, International Progeria Registry, and/or Medical and Research Database Program) collectively result in a variety of progerin-like proteins, resulting in various phenotypes (see Differential Diagnosis, Table 3, and Table 4).

Table 3.

Progeroid Laminopathy: Causative Allelic Variants and Clinical Features Compared to HGPS

Phenotype	Causative Variants in *LMNA*	Clinical Features Compared to HGPS	# of Affected Persons Identified	References
Progerin-producing progeroid laminopathy	c.1821G>A	Severe; neonatal progeria	2	Moulson et al [2007], PRF
	c.1868C>G	Mild	2	Fukuchi et al [2004], Shalev et al [2007]
	c.1968G>A	Very mild	2	Hisama et al [2011]
	c.1968+1G>C	Severe	2	Iqbal & Iftikhar [2008], PRF
	c.1968+5G>A	Very mild	1	Hisama et al [2011]

PRF = Progeria Research Foundation Diagnostic Testing Program

To date 18 referenced pathogenic variants causing progeroid laminopathies have been identified (see UMD-LMNA Mutations Database).

- Uniparental isodisomy of chromosome 1 (including *LMNA*) was identified in cultured cells of an individual with a progeroid phenotype. This was a mosaic rearrangement of chromosome 1 and a deletion involving the *LMNA* locus [Eriksson et al 2003]. It is not known whether this uniparental isodisomy was present in vivo.

- A child with the pathogenic variant c.433G>A in exon 2 of *LMNA* had atypical progeroid features including persistence of coarse hair over the head, ample subcutaneous tissue over the arms and legs, and severe strokes beginning at age four years [Eriksson et al 2003].

- One individual with the c.1868C>G *de novo* autosomal dominant pathogenic variant causing a 105-base pair deletion in exon 11, resulting in a 35-amino acid deletion and phenotype similar to but milder than HGPS. The affected man was normal at birth and developed a large head at age one year, growth failure at 12 years, and alopecia in later childhood [Fukuchi et al 2004]. He died of a myocardial infarction at age 45 years, having developed a progeroid phenotype.

- Restrictive dermopathy (OMIM 275210) has been associated with c.1699_1968del and a severe progeroid phenotype [Navarro et al 2004].

- Two Han Chinese siblings exhibited an autosomal recessive homozygous c.1579C>T pathogenic variant in *LMNA*. Both parents were heterozygous for this variant. The elder sibling, a female age ten years, showed a phenotype with overlapping features of HGPS and mandibuloacral dysplasia (MAD), including growth failure, hair, skin and skeletal features, left ventricular hypertrophy with a mild regurgitation of the tricuspid valve and pulmonary valve. Unlike HGPS, the distal phalanges of the second to fifth fingers were absent. The younger male sibling displayed some early physical changes in growth and skin by age six months [Xiong et al 2013].

- A family with an affected father and two sons displayed a heterozygous pathogenic variant c.667G>A in exon 4 of *LMNA* (reference sequence NM_170707.2). Phenotypes were similar to Dunnigan-type familial partial lipodystrophy, including atherosclerosis, insulin resistance, and hypertension in the proband (father) and dyslipidemia and hepatic steatosis in all the individuals heterozygous for the variant. The father died at age 45 years of complications of coronary angiography [Weterings et al 2013].

- One female child with a homozygous c.1303C>T *LMNA* pathogenic variant plus partial UPD of chromosome 1 displayed a severe phenotype of progeroid laminopathy with restrictive dermopathy-like features. These included total alopecia, stagnating weight and growth, progressive skin swelling and solidification, acrocontractures, osteolysis, and muscular hypotension. The affected individual died at the age of 11 months of global respiratory insufficiency [Starke et al 2013].

- A Chinese boy age two years exhibited a homozygous pathogenic variant c.1619T>C and uniparental disomy of chromosome 1. The mother was heterozygous for the variant and the father was not found to have the variant. Authors speculate that during maternal meiosis two recombination events, proximal and distal to *LMNA*, followed by nondisjunction, resulted in a gamete with two copies of chromosome 1 both containing the c.1619T>C pathogenic variant. The further loss of paternal chromosome 1 through trisomy rescue after fertilization led to homozygosity of the c.1619T>C variant. The phenotype was one of overlapping features of HGPS and MAD, including failure to thrive, total alopecia, joint contractures, hyperpigmentation with sclerosis of the skin, stiffness and blunting of the fingertips, prominent scalp veins, limited jaw mobility, dental crowding, acroosteolysis in the clavicles, hands, and feet, wormian bones, and osteopenia [Bai et al 2014].

- An adult male exhibited a heterozygous c.1771T>A variant in exon 11 of *LMNA* associated with an acrogeria syndrome. His phenotype at age 36 years included a thin nose; lipodystrophic distal lower limbs, hands, and feet; short clavicles; translucent pigmentation abnormalities; prominent veins; and osteolysis of the distal phalanges [Hadj-Rabia et al 2014].

Other laminopathies

- Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD)
- Autosomal recessive Emery-Dreifuss muscular dystrophy (AR-EDMD)
- Autosomal dominant familial dilated cardiomyopathy and conduction system defects (CMD1A) (see Dilated Cardiomyopathy)
- Autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD)
- Autosomal dominant limb-girdle muscular dystrophy 1B (LGMD1B) (see Limb-Girdle Muscular Dystrophy)
- A normal variant in *LMNA* (NM_170707.2:c.1908C>T) associated with obesity-related traits in Canadian Oji-Cree
- Autosomal recessive axonal neuropathy Charcot-Marie-Tooth disease 2B1 (CMT2B1)
- Autosomal recessive mandibuloacral dysplasia (MAD). A compound heterozygous pathogenic variant (NP_733821.1:p.[Arg471Cys]+ [Arg527Cys] in exon 8 and exon 9 respectively) in a 28-year-old woman with MAD, previously diagnosed as "atypical progeria," was reported [Cao & Hegele 2003].
- A family with four affected sibs with a homozygous pathogenic variant NM_170707.2:c.1626G>C (p.Lys542Asn) with many features of MAD, but some features of progeria as well [Plasilova et al 2004]
- Atypical Werner syndrome [Chen et al 2003]
- A single case report of a male heterozygous for the NM_170707.2:c.398G>T (p.Arg133Leu) pathogenic variant with lipoatrophy, disseminated white skin papules, hypertrophic cardiomyopathy, hepatic steatosis, and insulin resistance [Caux et al 2003]
- A single case report of a female heterozygous for the pathogenic variant NM_170707.2:c.428C>T (p.Ser143Phe) with myopathy, hypotonia, loss of subcutaneous tissue, osteopenia, and progressive spinal rigidity [Kirschner et al 2005]

Differential Diagnosis

In one report, a heterozygous pathogenic variant (NM_170707.2:c.1960C>T (p.Arg654Ter) in *LMNA* and homozygous pathogenic variant in *ZMPSTE24* (NM_005857.3), which encodes a post-translational prelamin A processing protein, resulted in a phenotype similar to progeroid laminopathy [Denecke et al 2006].

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

- Progerin-producing progeroid syndromes (see Genetically Related Disorders)
- Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) (OMIM 264090)
- Acrogeria (OMIM 201200)
- Cockayne syndrome
- Hallermann-Streiff syndrome (OMIM 234100)
- Gerodermia osteodysplastica (OMIM 231070)
- Berardinelli-Seip congenital lipodystrophy (congenital generalized lipodystrophy)
- Petty-Laxova-Weidemann progeroid syndrome (OMIM 612289)
- Ehlers-Danlos syndrome, progeroid form (OMIM 130070)
- Werner syndrome, atypical form
- Mandibuloacral dysplasia (See Genetically Related Disorders) (OMIM 248370)
- Nestor-Guillermo syndrome (OMIM 614008)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed Hutchinson-Gilford progeria syndrome (HGPS), the following evaluations are recommended:

- Weight and height plotted on standard growth charts to evaluate growth over time
- Baseline electrocardiogram (ECG) and echocardiogram
- Baseline carotid artery duplex scans to evaluate size of the lumen and intimal thickness in order to establish baseline vascular status
- Baseline MRI/MRA of the brain and neck
- Skeletal x-ray to evaluate for characteristic findings: acroosteolysis, clavicular resorption, coxa valga, and extraskeletal soft tissue calcifications [Cleveland et al 2012]
- Dual-energy x-ray absorptiometry (DEXA) to assess bone mineral density. Note: This must be normalized for height-age [Gordon et al 2011].
- Standard goniometry to assess joint mobility; physical therapy and occupational therapy assessments
- Nutritional assessment
- Audiologic, ophthalmologic, and dental examinations
- Medical genetics consultation

Treatment of Manifestations

A complete, system-based management guide is available from the Progeria Research Foundation.

No evidence that a low-cholesterol, low-fat, or other special diet influences the course of progeria exists. Thus, a regular diet is indicated unless the lipid profile becomes abnormal, at which point appropriate treatment includes exercise, diet modification, and medication as warranted. Frequent small meals tend to maximize caloric intake.

Stiffened peripheral vasculature may be less tolerant to dehydration; therefore maintaining optimal hydration orally is recommended.

Shoe pads are recommended, as lack of body fat leads to foot discomfort.

Use of sunscreen on all exposed areas of skin, including the head, is recommended for outdoor activities.

Prior to decline in cardiovascular or neurologic status (resulting from strokes, angina, or heart attacks), children should be encouraged to be as physically active as possible, taking into account possible limitations related to restricted range of motion of joints and hip problems including osteoarthritis and hip dislocation.

Because intellect and maturity are normal, age-appropriate schooling is usually indicated.

Infections are generally handled as for unaffected children.

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 is present.

Statins are recommended for their putative effect on farnesylation inhibition.

Anticoagulation is warranted if vascular blockage, transient ischemic attacks, stroke, angina, or myocardial infarction occur.

Injuries. Wound healing is normal.

Fracture rate is equivalent to the general pediatric population. When children do fracture, treatment and healing are routine.

Hips. Conservative management of hip dislocation with physical therapy and body bracing and avoidance of surgical procedures on bones are recommended when possible.

Teeth. Extraction of primary teeth may be required to avoid crowding and development of two rows of teeth. Since secondary teeth may erupt slowly or not at all, pulling primary teeth to make room for secondary teeth should be performed after secondary teeth have fully or almost fully or almost fully descended. Once the primary tooth has been extracted, the secondary tooth often moves into the appropriate position with time.

General anesthesia and intubation should be performed with extreme caution, ideally with fiberoptic intubation, if possible. Individuals with HGPS may have a narrow and unusually shaped airway; additionally, they may exhibit an extreme sensitivity to alterations in blood pressure due to vascular stiffness.

Physical therapy. Routine physical and occupational therapy is recommended to help maintain range of motion in large and small (i.e., finger) joints; see Physical Therapy and Occupational Therapy in Progeria (pdf). Active stretching and strengthening, along with hydrotherapy, are recommended.

Podiatric evaluation is indicated to determine if shoe inserts are needed

Eye care. Corneal dryness, clouding or ulceration should be fully evaluated by an ophthalmologist. Exposure keratitis primarily caused by nocturnal lagophthalmos can be treated during daytime with ocular lubication and during sleep with moisturizing ointment or by closing eyelids with skin tape.

Hearing loss. Hearing aids can be used, when clinically necessary.

Prevention of Secondary Complications

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 low-dose aspirin treatment, at doses of 2-3 mg/kg body weight per day. Note: 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.

Adequate oral hydration is recommended, as the vasculature becomes generally less pliable and the risks of stroke and cardiac complications increase over time due to decreased vascular compensation. This is especially important during hot weather or airplane travel.

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 all immunizations are recommended. Immunizations are generally handled as for unaffected children.

Surveillance

The following are appropriate:

- ECG, measurement of blood pressure, echocardiogram, and carotid duplex scans annually or semi-annually to monitor for cardiovascular disease. Note: Children may experience severe carotid artery atherosclerotic blockage prior to any significant ECG changes.
- Annually:
    - Neurologic assessment
    - MRI/MRA of head and neck to assess for vascular changes and silent strokes, which are true strokes that do not result in any clinical symptoms
    - Lipid profiles
    - Dental examination, x-ray, and cleaning
    - Hip x-rays to evaluate for avascular necrosis and progressing coxa valga
    - Dual x-ray absorptiometry (DXA) and/or peripheral cutaneous computed tomography scan of spine, hips, and total body to assess bone density and body fat composition
    - Physical therapy and occupational therapy assessment for joint contractures and activities of daily living
    - Complete audiologic assessment with special attention to possible low-frequency conductive hearing loss
    - Complete ophthalmologic examination with special attention to possible exposure keratopathy

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. Physical activity should be self-limited.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search HGPS or progeria within ClinicalTrials.gov for access to information on clinical trials for HGPS.

The three therapies currently under human clinical trial investigation for HGPS include: lonafarnib, pravastatin, and zoledronate. For each of these drugs, the target action in HGPS is to inhibit post-translational farnesylation of progerin, the active disease-causing protein in HGPS (see Figure 1).

- Lonafarnib is an investigational farnesyltransferase inhibitor.
- Pravastatin inhibits HMG-CoA reductase.
- Zoledronate is a bisphosphonate that inhibits farnesyl pyrophosphate synthase.

Three clinical trials have been conducted: lonafarnib monotherapy; lonafarnib in combination with pravastatin and zoledronate; and pravastatin and zoledronate administered as combination therapy:

- Clinical trial results for lonafarnib have revealed improvement in the rate of weight gain, vascular distensibility as measured via pulse wave velocity and vascular echodensity, bone rigidity, neurosensory hearing [Gordon et al 2012], headaches [Ullrich et al 2013], and life span [Gordon et al 2014].
- Trial results for pravastatin and zoledronate are not yet known.

Treatments proposed through preclinical studies but not tested in humans:

- Rapamycin improved cellular phenotypes in HGPS fibroblasts via increased autophagy [Cao et al 2011, Cenni et al 2011] and extends life span in a lamin A-deficient mouse model.
- Antisense oligonucleotides [Osorio et al 2011] reduced progerin protein levels, enhanced life expectancy, improved disease phenotype, and improved cellular phenotypes in an HGPS mouse model.
- Resveratrol [Liu et al 2012] improves the cellular phenotype in HGPS fibroblasts, improves lamin A function via a SIRT-1 dependent manner and extends life span in a *Zmpste24*$^{-/-}$ mouse model.
- Nat10 inhibition by a chemical named remodelin that is not yet developed for clinical use corrected phenotypes in HGPS fibroblasts [Larrieu et al 2014].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hutchinson-Gilford progeria syndrome (HGPS) is typically caused by a *de novo* autosomal dominant pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all individuals with HGPS have the disorder as the result of a *de novo* pathogenic variant.
- One person with HGPS resulting from apparent somatic and germline mosaicism in an asymptomatic parent has been reported [Wuyts et al 2005].
- Parents of probands are not affected.

Sibs of a proband

- Because HGPS is typically caused by a *de novo* pathogenic variant, the risk to the sibs of a proband is small.
- One instance of apparent somatic and germline mosaicism has been reported [Wuyts et al 2005]. Therefore, the risk to sibs of a proband is estimated to be one in 500.
- 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 HGPS.

Offspring of a proband. Individuals with classic HGPS are not known to reproduce; information about individuals with atypical HGPS is limited.

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

Related Genetic Counseling Issues

Origin of *de novo* pathogenic variant. At least one *LMNA* pathogenic variant has been paternal in origin, though the number of families evaluated is small [Eriksson et al 2003]. The pathogenic variant was maternal in origin for the case of mosaicism reported by Wuyts et al [2005]. A paternal age effect is present as the father's age is significantly increased by about five years on average [Brown et al 1985]. There is no increase in consanguinity.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

If the *LMNA* pathogenic variant has been identified in an affected family member, prenatal testing or preimplantation genetic diagnosis for a pregnancy at increased risk for HGPS may be an option that a couple may wish to consider.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

Molecular Genetics

Molecular Basis of Disease

Lamin A is an inner nuclear membrane protein with both structural and cell signaling effects. The single C to T transition at nucleotide 1824 of *LMNA* does not change the translated amino acid (p.Gly608Gly), but activates a cryptic splice site, resulting in the deletion of 150 base pairs in the 3' portion of exon 11. Translation followed by post-translational processing of this altered mRNA produces a shortened abnormal prelamin A protein with a 50 amino-acid deletion near its C-terminal end, henceforth called "progerin." The 50 amino-acid deletion removes the recognition site that leads to proteolytic cleavage of the terminal 18 amino acids of prelamin A, along with the phosphorylation site(s) involved in the dissociation and re-association of the nuclear membrane at each cell division.

A key component of disease in HGPS is the presumably persistent farnesylation of progerin, which renders it permanently intercalated into the inner nuclear membrane where it can accumulate and exert progressively more damage to cells as they age. That the failure to remove the farnesyl group is at least in part responsible for the phenotypes observed in HGPS is strongly supported by studies on both cell and mouse models which have either been engineered to produce a non-farnesylated progerin product or treated with a drug that inhibits farnesylation, rendering a non-farnesylated progerin product.

Non-progerin producing *LMNA* variants result in abnormal lamin A proteins with variable abnormalities in their structure and function, including interactions with the nuclear membrane, lamin-associated proteins, all of which produce cellular and organismal diseases with varying phenotypes that overlap with HGPS in some aspects.

Gene structure. The coding region of *LMNA* spans approximately 24 kb and contains 12 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. A recurrent *de novo* single-nucleotide variant of a single-base substitution, a c.1824C>T transition that is a silent variant and does not change the glycine amino acid at codon 608 within exon 11 in *LMNA*, was found in 18 of 23 individuals with a clinical diagnosis of HGPS [Eriksson et al 2003] and independently in two of two individuals studied by De Sandre-Giovannoli et al [2003] [De Sandre-Giovannoli & Lévy 2006].

One of 25 individuals had a c.1822G>A change at codon 608 (p.Gly608Ser) also leading to the same internal splice effect that produced progerin (protein product of *LMNA*), plus a normally spliced variant protein with an amino acid substitution [Eriksson et al 2003]. It is likely that both the progerin and lamin A c.1822G>A variant contributed to disease, as this child had a more severe disease phenotype than HGPS.

Two individuals with a heterozygous transition pathogenic variant c.1961+1G>A have been reported; one died at age 3.5 years of gastroenteritis and pneumonia [Moulson et al 2007] and the other died at age six months [Navarro et al 2004]. This pathogenic variant creates a cryptic splice donor sequence that produces an estimated 4.5-fold increase in progerin production versus classic HGPS [Moulson et al 2007].

One individual with a heterozygous transition variant c.1821G>A has been reported. The individual had a more severe progeroid phenotype than HGPS, and died at age 26 days of unspecified genodermatosis with interstitial pneumonia [Moulson et al 2007]. This variant creates a cryptic splice donor sequence that results in an estimated twofold increase in progerin production compared to classic HGPS [Moulson et al 2007, Reunert et al 2012].

A 6-Mb deletion spanning *LMNA* was reported in an affected individual [Eriksson et al 2003]. Of note, the 6-Mb deletion is not in itself considered pathogenic. It was hypothesized that the individual was originally heterozygous for a pathogenic codon 608 *LMNA* variant and this allele later underwent an *LMNA* deletion. This phenomenon was referred to as a “somatic rescue” event. This deletion was discovered in vitro. The in vivo mutational status is unknown.

Table 4.

LMNA Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.433G>A	p.Glu145Lys	NM_170707.2 NP_733821.1
c.667G>A	p.Glu223Lys	
c.1303C>T	p.Ala435Cys	
c.1579C>T	p.Arg527Cys	
c.1619T>C	p.Met540Thr	
c.1961+1G>A		
c.1699_1968del	p.Gly567_Gln656del	
c.1771T>A	p.Cys591Ser	
c.1821G>A	p.Val607Val	
c.1822G>A	p.Gly608Ser	
c.1824C>T [1]	p.Gly608Gly	
c.1968G>A	p.Gln656Gln	
c.1968C>G	p.Thr623Ser	
c.1968+1G>A	(Splice donor site variant)	
c.1968+1G>C	(Splice donor site variant)	
c.1968+2T>A	(Splice donor site variant)	
c.1968+2T>C	(Splice donor site variant)	
c.1968+5G>C	(Splice donor site variant)	
c.1968+5G>A	(Splice donor site variant)	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. In-frame, exon 11 cryptic splice site activation variant

Normal gene product. The nuclear lamina is a protein-containing layer attached to the inner nuclear membrane. In mammals, it is composed of a family of polypeptides, with the major components being the lamins A, B1, B2, and C, with molecular weights ranging from 60,000 to 78,000. Lamins A and C are formed by alternative splicing of the *LMNA/C* gene transcript. Splicing within exon 10 gives rise to lamin C, whereas transcription of all 12 exons gives rise to lamin A. Lamins B1 and B2 are encoded by separate genes and there are no known progeroid pathogenic variants within lamins B1 and B2.

Lamin A is normally synthesized as a precursor molecule (prelamin A), and undergoes a four major post-translational processing steps. First, because prelamin A contains a CAAX (cysteine / aliphatic / aliphatic / any amino acid) box at its carboxyl terminus, it is modified by farnesylation. Following farnesylation, cleavage of the last three amino acids, methylation of the C-terminus, and internal proteolytic cleavage occur. Removal of the last 15 coding amino acids along with the CAAX box and farnesyl group generates mature lamin A with 646 amino acids.

Abnormal gene product. The HGPS-causing variants in codon 608 of *LMNA* leads to activation of a cryptic splice site within exon 11, resulting in production of a prelamin A that lacks 50 amino acids near the C terminus [Eriksson et al 2003]. The c.1824C>T pathogenic variant and consequent abnormal splicing produces a prelamin A that still retains the CAAX box and is therefore farnesylated, but is missing the site for endoproteolytic cleavage of the final 16 amino acids along with the farnesyl moiety that normally occurs during the final step in post-translational processing. The resulting protein, named progerin, is shortened and farnesylated. Since the lipophilic farnesyl moiety is utilized to anchor prelamin (and hence progerin) into the inner nuclear membrane, the lack of farnesyl cleavage likely results in permanent progerin intercalation within the nuclear membrane.

Click here for information on preclinical studies in HGPS cells and murine models.

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Chapter Notes

Author Notes

Dr. Gordon is involved in progeria clinical treatment trials being conducted at Children's Hospital Boston. For more information please contact Dr. Gordon at Leslie_Gordon@brown.edu.

Revision History

- 8 January 2015 (me) Comprehensive update posted live
- 6 January 2011 (me) Comprehensive update posted live
- 10 August 2006 (me) Comprehensive update posted to live Web site

- 30 July 2004 (cd) Revision: Prenatal Testing
- 11 February 2004 (wtb) Revision: sequence analysis of entire coding region now available
- 12 December 2003 (me) Review posted to live Web site
- 31 July 2003 (wtb) Original submission

Figures

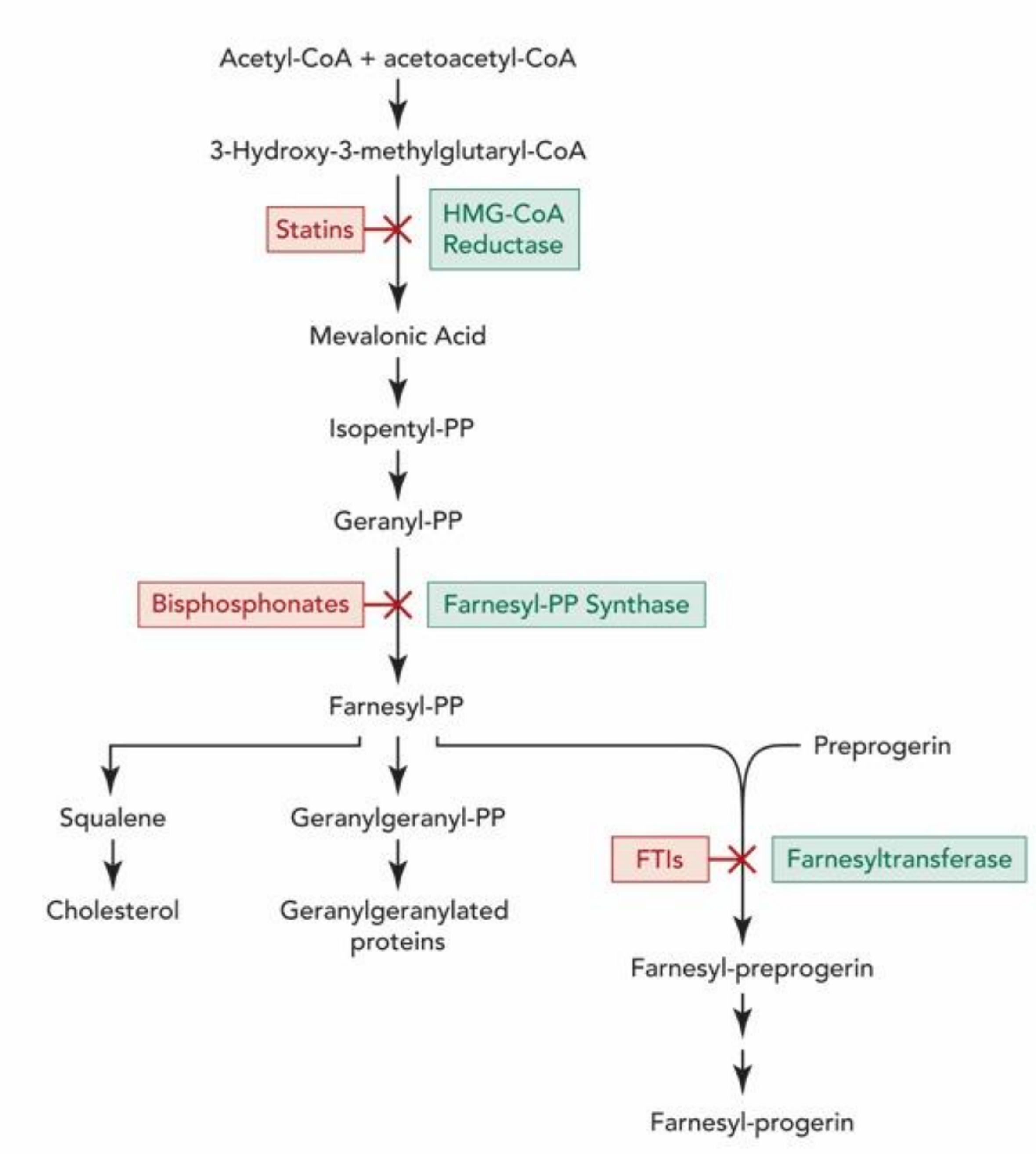

Figure 1.

Medications that inhibit the farnesylation of progerin

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