

Hutchinson Gilford Progeria

Zoya Kamal Khan

1st Year BDS, Islamabad Medical and Dental College, Islamabad, Pakistan

Key points:

- Molecular Pathogenesis
- Symptoms
- Pathophysiology
- Diagnosis and treatment
- Prognosis
- Conclusion

Introduction:

Hutchinson-Gilford Progeria Syndrome ("Progeria", or "HGPS") is a rare, fatal genetic condition characterized by an appearance of accelerated aging in children. Its name is derived from the Greek which means "prematurely old." It is named after the doctors who first described it in England; in 1886 by Dr. Jonathan Hutchinson and in 1897 by Dr. Hastings Gilford. In this disease the aging process of the body accelerates much faster than what it does in normal humans. It is a rare, lethal genetic disorder with an incidence of approximately one in four million live births¹.

Molecular Pathogenesis and Cause:

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disorder caused by a de novo (2), single nucleotide mutation (c.1824C>T) in the LMNA gene, which normally produces lamins A and C (proteins that support the nuclear envelope). Although the mutation doesn't change the amino acid, it activates a hidden (cryptic) splice site, which affects only lamin A and not lamin C. This abnormal splicing results in the production of progerin, a defective form of lamin A that lacks 50 amino acids³, including a critical site needed for proper protein processing.

Background: prelamins A and its modifications

Prelamin A is a precursor protein that becomes lamin A, at the end of prelamins A is a CAAX motif, a sequence of four amino acids: C= cysteine, A= two aliphatic amino acids, X= any amino acid like methionine or serine. An enzyme called farnesyltransferase (FTase) attaches a 15-carbon lipid called farnesyl group to the cysteine in the CAAX motif, this helps anchor the protein to the inner nuclear membrane and after farnesylation, the last three amino acids (AAX) are cleaved off. The cysteine gets methylated to help further anchor it. Uniquely, a second cleavage occurs by an enzyme called ZMPSTE24, it cuts off the last 15 amino acids including the farnesyl group, this releases prelamins A from the nuclear membrane so it can integrate into the nuclear lamina properly as lamin A⁴. In HGPS, progerin can be farnesylated but due to the internal deletion of amino acids 606-656 the ZMPSTE24 enzyme can't recognize it for final cleavage⁴. As a result, progerin keeps its farnesyl group and stays stuck to the nuclear membrane (remains permanently farnesylated and methylated), causing it to build up and damage the nuclear structure leading to the premature aging symptoms in children.³ Progerin behaves in a dominant negative fashion leading to a variety of cellular and molecular changes which includes nuclear abnormalities, defective DNA damage response (DDR) and DNA repair, accelerated telomere attrition.²

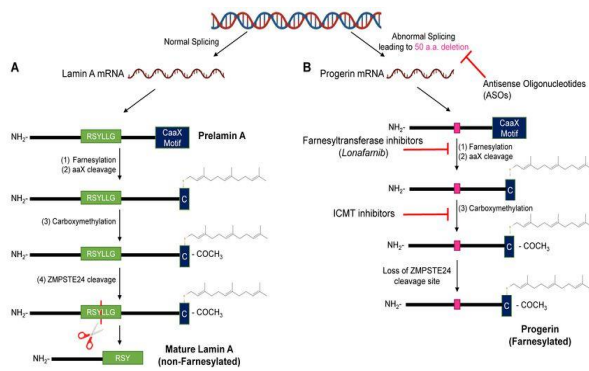


Figure 1: The differences between processing/modifying a normal prelamina A protein and the progerin mutant.²

Symptoms

Symptoms include a distinctive face, prominent eyes, leg and scalp veins, a senile appearance, loss of eyebrows, eyelashes, and scalp hair (alopecia), micrognathia, stunted growth, and sclerodermatous changes⁵.

Others include;

- Acanthosis of the epidermis
- Thickened collagen bundles in the dermis
- Abnormal mandibular condyles
- Cox Valga
- Hypoplastic articular eminences¹

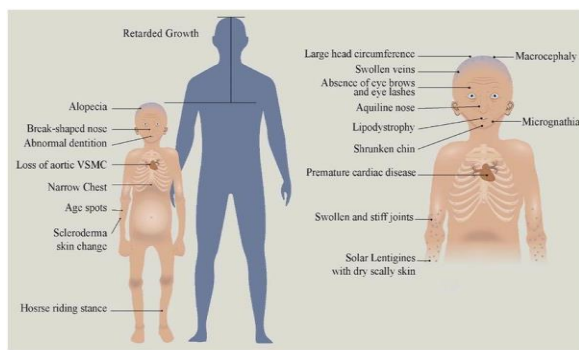


Figure 2: Clinical manifestations of Hgps.⁵

Cardiovascular Complications

HGPS is marked by rapid premature aging and accelerated development of cardiovascular disease, which is primary cause of death in affected individuals. Around 90% of deaths are due to cardiac infarctions, often resulting from extensive atherosclerosis, chronic low-grade inflammation, oxidative stress, and fibrosis. Progerin accumulation in coronary arteries significantly worsens cardiovascular outcomes by disrupting vascular integrity and cardiac electrophysiology. Common heart complications can include bradyarrhythmias, heart block, and ventricular arrhythmias, often linked to myocardial fibrosis and autonomic dysfunction, which increase the risk of sudden cardiac death. Vascular calcifications are also common, caused by a deficiency in extracellular pyrophosphate and worsened by loss of vascular smooth muscle cells (VSMCs) and vessel stiffening⁵.

Oral health and Dentition

Individuals with HGPS experience various oral anomalies, including hypodontia (missing teeth), ankyloglossia (restricted tongue movement), ogival palate (higharched palate), double rows of teeth, and delayed tooth eruption in both primary and permanent teeth. Teeth also tend to become crowded because of the abnormal growth and positioning of the maxilla and mandible. In addition, circumoral cyanosis (bluish discoloration around the mouth) is observed.⁵

The mandible shows abnormalities like an obtuse mandibular angle and short ramus, while the alveolar process (the part of the jaw where teeth sit) is atrophic. The palatal vaults are high and narrow and because the maxillary arch is short, there is a general craniofacial imbalance.⁵

Skeletal Abnormalities

The syndrome associated with typical bone and joint abnormalities in progeria patients is known as Hutchinson–Gilford Skeletal dysplasia. Some of the anomalies include narrow ribs, small clavicles, and acroosteolysis.⁵

Avascular necrosis in patients is due to vascular impairment, especially in the femoral head. Skeletal abnormalities associated with HGPS can involve mandibular and cranial dysplasia with haphazard growth, possibly implicating osteogenesis defects, particularly in extremities.⁵

Diagnosis

The diagnostic criteria for HGPS is Phenotype recognition combined with a progerin producing mutation in the LMNA gene, either at the exon 11 intronic border (atypical form) or within exon 11 (classic form)⁵.

Your child's healthcare provider may be able to diagnose your child's condition based on their physical appearance. A physical exam would be performed and you'll be asked about your child's symptoms. If they suspect progeria, they can use genetic testing to confirm the diagnosis. The test requires taking a blood sample from your child. ¹

Treatment

Farnesyltransferase inhibitors (FTIs) are promising therapeutic agents for Hutchinson–Gilford Progeria Syndrome (HGPS). These small molecules work by blocking the farnesylation of progerin, a key step in its integration into the nuclear membrane, therefore improving nuclear morphology in cells and reducing disease markers in lab and animal models⁵.

Lonafarnib is an orally active FTI approved by the FDA in 2020, it is the first approved treatment for HGPS. It has been shown to improve bone strength, hearing, and cardiovascular stiffness, and provides significant symptomatic improvement in cardiac health, which is crucial since heart damage is the leading cause of death in HGPS.⁵

References

1. Vijendra Rathod A, Sandeep Lembhe S, Balkrushna Thombre S, Satish Khandagle S, Nandkishor Dhone M, Prakash Vaishnav P.
2. Batista N, Desai S, Perez A, Finkelstein A, Radigan R, Singh M, Landman A, Drittell B, Abramov D, Ahsan M, Cornwell S Zhang D.
3. Macicior J, Marcos-Ramiro B, Ortega-Guitierrez S.
4. Lamis A, Siddiqui S, Ashok T, Patni N, Fatima M, Aneef A. National Library of Medicine. pub med central.
5. Arun A, Nath A, Thankachan B, Unnikrishnan M.

Triple therapy is another effective treatment, it is a combination of lonafarnib, pravastatin, and zoledronate. This regimen targets multiple pathways involved in the disease, preventing both progerin buildup and bone deterioration. Clinical trials have shown this approach can increase survival by an average of 1.6 years, with about 71% of patients showing measurable improvements in either carotid artery health or weight gain.⁵

Prognosis

The hallmark of the disease is very early aging with an expected average life span of about 15years. HGPS is progressive, children usually die primarily from premature atherosclerotic cardiovascular disease as a result of progerin accumulation, which leads to a wide range of disease phenotypes and death from vascular events may occur before age 10.⁵

Conclusion

HGPS is a "premature aging" condition in which children show phenotypes that may reveal information about the aging process at both the cellular and organismal levels. Progeria research has resulted in an increasing number of intriguing treatment possibilities and it also provides a unique model for clarifying new lamin A/C and progerin roles in the cell. It is worth noting that in HGPS preclinical investigations, a drug's potential to selectively choose the cardiovascular system should be assessed, as it is the disorder's main functional aim, resulting in premature death. Cardiovascular measurements would also be selected among treatment efficacy readouts.⁴ With an emphasis on creating therapies and a cure for this very illness, the Progeria Research Foundation has been at the forefront of research and clinical trials.⁵