Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome: Clinical Signs, Molecular Causes, Treatments, and Insights into the Aging Process

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is a condition characterized by signs of accelerated aging that present within the first year of life. Notable characteristics of children with HGPS include prominent superficial veins, failure to thrive, alopecia, as well as various skeletal and cardiovascular pathologies normally associated with advanced age. The discovery of the lamin A (C to T) gene mutation at position 1824 of the coding sequence has ushered in a greater understanding on the essential role of lamin A protein processing. In normal cells, processing prelamin A to mature lamin A is complete following the cleavage of end terminal amino acids. In HGPS, gene mutation results in the deletion of a Zmpste24/FACE1 splice site in prelamin A, preventing end terminal cleavage. Thus, prelamin A remains anchored due to C-terminal farnesylation. Lamin A eventually accumulates within the inner nuclear membrane of cells, resulting in disease pathology. The generation of experimental mouse models to understand the role of lamin A in normal, and HGPS cells have fostered the development of prospective HGPS treatments. Clinical trials investigating farnesyltransferase inhibitors (FTIs), statins, and bisphosphonates as HGPS treatments are currently underway. HGPS and the relationship to lamin A has also shed light on normal aging as accumulation of prelamin A has been revealed in aged (non-HGPS derived) cells.

KEYWORDS: *progeria, lamin A, laminopathy, farnesylation, aging*

INTRODUCTION

Aging is an inevitable process of bodily changes that eventually results in decreased physiologic capacity, decreased ability to maintain homeostasis, and increased vulnerability to disease processes. These changes generally occur later in life. However, in one out of every four to eight million births, children are born with HGPS and symptoms of age-related diseases such as skin thinning, low bone density, and cardiovascular complications that occur within the first decade of life. This early onset of aging in HGPS is different from other inherited accelerated aging disorders such as Werner's syndrome, which typically presents later in life (after puberty).

CLINICAL FEATURES OF HGPS

First described in 1886 by Dr. Jonathan Hutchinson,[1] Dr. Hastings Gilford subsequently expanded on Hutchinson's observations and derived the word "progeria" from ancient Greek origins ("pro" from the Greek word for "before" or "forward" and "geron" meaning "old person") to describe this accelerated aging syndrome.[2]

As of December 2010 there were approximately 78 known children with HGPS in the world, two living in Canada.[3] Children with HGPS are born with normal appearance and weight.[4] Within 12 months, clinical symptoms appear sporadically and continue to appear throughout life (Figure 1). The first noticeable signs of HGPS are circumoral cyanosis (a blue tint to the skin surrounding the lips) and a visible vein across the nasal bridge.[4,5] Children present initially with failure to thrive, and in their first to third of year of life, skin complications, hair loss (also known as alopecia), and joint deformities become apparent.[4,5] Auditory and endocrine dysfunctions are eventually noted.

Within the first year, growth is disturbed, with weight more affected than height. Pitting edema (slight swelling due to fluid build-up in the tissues) is seen in the lower abdomen, upper gluteal area, genitalia, and anterior thighs.[4,5] Pitting edema can arise anywhere from one and a half months to two years, taking on

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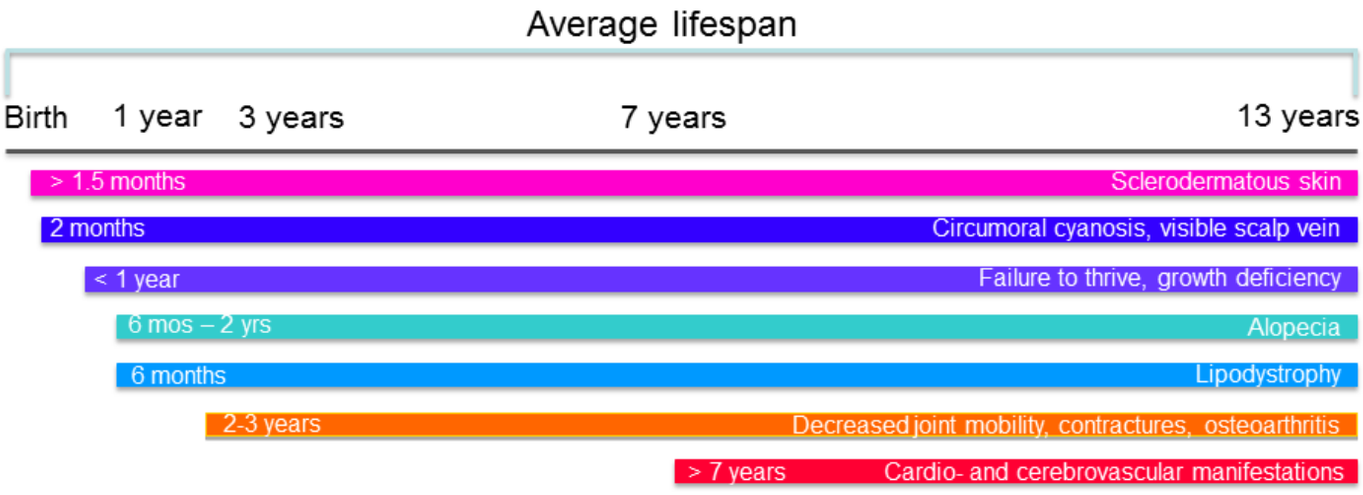

Figure 1. Common clinical signs of HGPS and typical time of presentation.

a thick, tight, stiff quality with time.[5] Alopecia usually takes place within six months to two years, and between the ages of two and three years, most children become bald with the exception of fine, downy hair.[4,5] Lipodystrophy, the disappearance of subcutaneous fat and thinning of the skin, is noted at as early as six months and contributes to the appearance of prominent veins throughout the child's body. This is first seen over the nasal bridge, then the body and infraorbital regions, giving rise to the appearance of prominent eyes.[5] Progressive resorption of bone, also known as osteolysis, of the distal phalanges tends to start between one and two years of age in the index and little fingers. Skin overlying the fingertips becomes red and swollen without pain.[5] Osteolysis of the acromial ends of the clavicles and upper ribs eventually results in characteristic narrow shoulders and pear-shaped thorax.[5] Joint range of mobility declines around age two or three years. Children with HGPS eventually possess a wide-based, shuffling gait resulting from hip deformities and knee joint stiffness.[4]

HGPS-affected children have normal mental and motor development, display age-appropriate behaviour, and are very alert and cheerful.[5] Low-conduction hearing loss and endocrine dysfunction occur later in life.[4] Children with HGPS fail to develop secondary sexual characteristics. Insulin resistance occurs in about 50 % of affected patients without progression to diabetes mellitus.[6]

Although the onset of specific abnormalities varies considerably, the major health concern for children with HGPS is progressive atherosclerosis of the coronary and cerebrovascular arteries.[4,5,7–9] Stiffness of the blood vessels manifests clinically as elevated systolic and diastolic blood pressure. Chest pain or congestive heart failure can also occur.[6] Demise is largely a result of cardiac or cerebrovascular-related events, such as myocardial infarction or stroke.[4] These events tend to occur after age seven,[10] although strokes and transient ischemic attacks, or 'mini-strokes', have occurred in children with HGPS as young as age four.[6]

Other early distinguishing physical features include the following: sleeping with eyes open, thin lips, a small and receding lower jaw, nearly normal neurocranial growth paralleling brain growth, and a narrow nasal bridge with a sharp nasal tip.[5,6] Ultimately, diagnosis is based on recognition of the aforementioned clinical features and is confirmed with molecular genetic testing.[6]

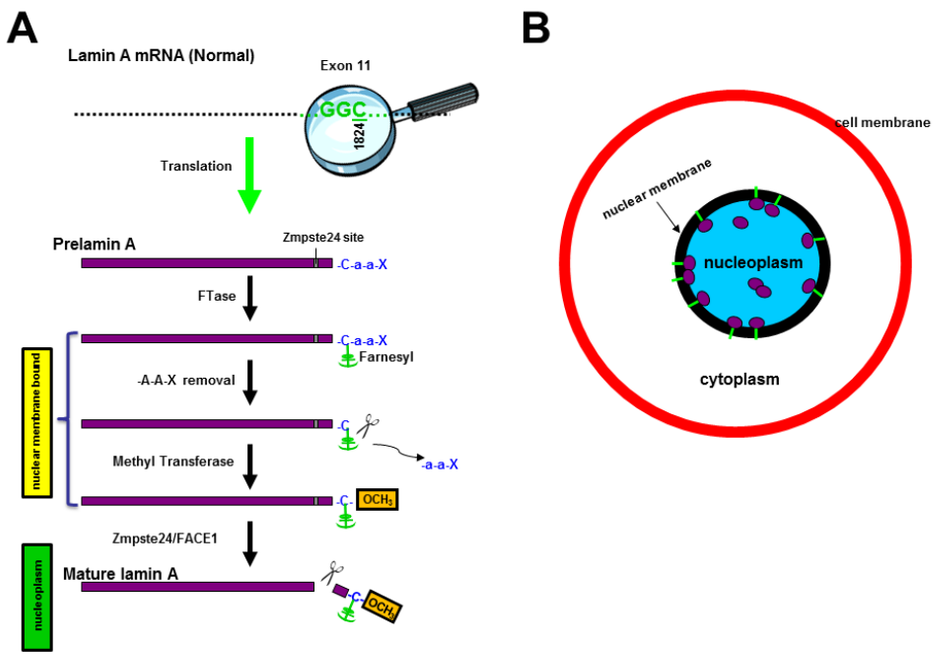

Figure 2. Normal processing of lamin A from mRNA to mature lamin A. (A) Normal lamin A mRNA is translated to prelamin A. Prelamin A becomes farnesylated resulting in anchoring to the inner nuclear membrane. Zmpste24/FACE1 cleavage of terminal amino acids results in release from the nuclear membrane and localization to the nucleoplasm. (B) In normal processing, prelamin A exists anchored to the nuclear membrane and is finally cleaved by Zmpste24/FACE1 to produce mature lamin A which localizes to the nucleoplasm.

MOLECULAR BACKGROUND OF HGPS

Lamins are intermediate filament proteins

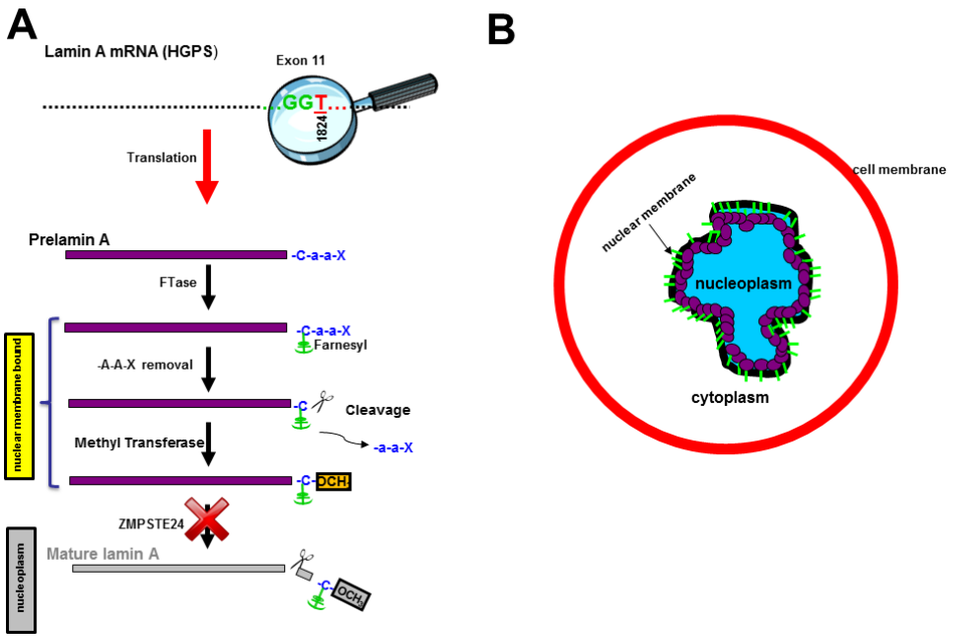

Figure 3. Processing of lamin A in cells from patients with HGPS. (A) Mutated laminA mRNA is translated to prelamin A that does not contain Zmpste24/FACE1 cleavage site. PrelaminA then becomes farnesylated resulting in anchoring to the inner nuclear membrane. The absence of Zmpste24 cleavage of terminal amino acids results in the inability to generate mature lamin A. (B) In cells from patients with HGPS prelamin A remains farnesylated, accumulates at the inner nuclear membrane, and results in misshapen nuclei.

forming a network in the inner nuclear membrane. They not only play an essential role in maintaining the structural integrity of the nucleus but are also involved in chromatin organization, DNA replication/transcription, and RNA processing.[11] There are type A (lamin A) and type B (lamin B) lamins. In contrast to lamin A, which is only expressed in differentiated tissues, lamin B is expressed throughout development, including gastrulation. Thus, defects in lamin B are generally lethal.[12] Various defects in lamin A can result in a wide variety of laminopathies. HGPS is the most severe of the (at least) sixteen laminopathies. In terms of HGPS classification,[13] HGPS falls into a group of systemic laminopathies that includes other diseases such as Werner's syndrome. These particular laminopathies affect a variety of tissue types. On the other hand, non-systemic or tissue-restricted laminopathies are classified based on the specific tissue affected. Muscle type laminopathies, such as in Emery-Dreifuss muscular dystrophy, are characterized by muscle wasting. Lipodystrophy laminopathies, including Dunnigan familial partial lipodystrophy, are characterized by abnormal fat distribution. Neuropathic laminopathies, such as Charcot-Marie-Tooth disease type 2B1, affect nerves. The molecular causes of the various laminopathies are quite diverse with over 340 unique mutations from over 1000 different patients. These mutations affect genes encoding lamins, associated with lamin post-translational modification, or proteins that interact with lamins. Specifically in HGPS, there is aberrant lamin A protein maturation.[14]

In normal lamin A maturation, the newly translated prelamin A protein undergoes a series of post-translational modifications to form mature lamin A (Figure 2a).[15] The C-terminal end of prelamin A contains a cysteine-aliphatic-aliphatic-any amino acid (CaaX) motif prompting prenylation, a process of C-terminal lipidification. Prenylation generally occurs through the addition of a farnesyl group to the cysteine residue in CaaX via farnesyltransferase (FTase). Subsequently, the –aaX tripeptide is enzymatically released. The remaining farnesylcysteine is then methylated through methyl transferase. The addition of a farnesyl– and methyl– group increases the hydrophobicity of lamin A,[16] which aids in prelamin A association with the nuclear membrane. In the last step of maturation, the end 15 amino acids of prelamin A are cleaved by a zinc metalloproteinase (Zmpste24; also known as FACE1), and mature lamin is formed. The removal of the terminating 15 amino acids allows for lamin A detachment from the nuclear membrane.[17]

While numerous causal mechanisms exist in HGPS, 90 % of affected children have a de novo heterozygous single cytosine to thymine point mutation (GGC to GGT) in exon 11 at position 1824 of the coding sequence (Figure 3a).[14,18] The mutation generates a cryptic splice site, resulting in a transcript 150 base pairs shorter than normal and 50 fewer amino acids translated. The necessary sites for Zmpste24 cleavage are among the 50 amino acids not translated. Farnesylated prelamin A consequently anchors to the nuclear envelope. However, full maturation is incomplete as Zmpste24 cleavage of the end terminal amino acids does not occur. Ultimately, prelamin A accumulates in the nuclear envelope, disrupting nuclear integrity and nuclear shape (Figure 3b). Nuclei appear larger, distorted, blebbed, and have a thicker nuclear lamina.[19] The mechanical properties of the nuclear lamina in HGPS cells are compromised. The nuclei are stiffer, have reduced deformability,[20] and do not respond to mechanical force in the same manner as normal cells.[21] Consequently, cell proliferation, differentiation, and gene expression are affected in HGPS cells.[22,23] Such marked deficiencies in general cellular processes caused by aberrant lamin A may explain how a single mutation affects various tissues. As well, studies in skin,[24] bone,[25] and cardiovascular tissues,[5,8,26,27] further exemplify the importance of normal lamin A regulation in specific tissue homeostasis.

POTENTIAL TREATMENTS FOR HGPS

Prior to the HGPS gene discovery, treatments were limited and unsuccessful. For instance, nutritional and growth hormone therapy resulted in only transient improvements in individuals with HGPS.[28] More recently, various mouse models have been generated, allowing for an enhanced general understanding of lamin A as well as providing insights into potential HGPS treatments.

Mouse lines absent in the lamin A Zmpste24 cleavage sites or Zmpste24 deficient mice demonstrate HGPS-like symptoms,[29,30] illustrating the importance of Zmpste24 cleavage and the deleterious effects of sustained farnesylated prelamin A. Thus, a potential therapeutic approach involves treatment

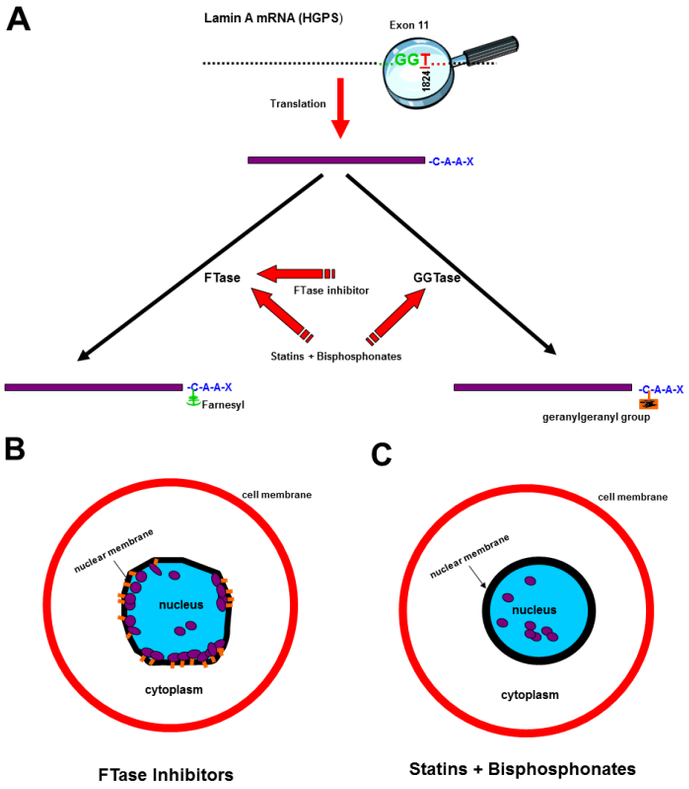

Figure 4. Prelamin A has alternative routes of prenylation. (A) Prelamin A can become farnesylated via farnesyltransferase (FTase) or geranylgeranylated via geranylgeranyltransferase (GGT). Farnesyltransferase inhibitors are able to inhibit farnesylation but not geranylgeranylation and results in (B) an overall improvement in nuclear membrane shape in HGPS (or HGPS-like) cells. (C) Statins and bisphosphonates are able to inhibit farnesylation and geranylgeranylation and may result in a greater improvement of nuclear membrane organization.

with farnesyltransferase inhibitors (FTIs) to prevent prelamin A anchoring to the nuclear membrane. Interestingly, exposure of HGPS cells to FTIs appeared to prevent prelamin A from anchoring to the nuclear membrane. Rather, FTI treatment localized prelamin A to the nucleoplasm and resulted in improved nuclear shape (Figure 4a, b)[31,32] as well as recovered nuclear stiffness in HGPS cells.[21] Additional studies reveal that in mouse models of HGPS, FTIs improved bone quality, growth, and survival.[33–35] Such findings have led to the first HGPS treatment clinical trials with the FTI, lonafarnib (Sarasar), to investigate the efficacy of FTIs as treatments for HGPS.[36] Lonafarnib is not commercially available in Canada or the United States and can only be administered in approved clinical trials.

Though FTIs appear to prevent the farnesyltransferase-based prenylation (lipidification) necessary to anchor prelamin A to the nuclear membrane (Figure 2), some concern arises with the finding that FTI treatments may result in an alternative route of prelamin A prenylation known as geranylgeranylation. Geranylgeranylation is a process by which a lipophilic geranylgeranylisoprene unit is added to the C-terminal of proteins via geranylgeranyltransferases (GGTase; Figure 4a).[37] Thus, geranylgeranylation is an alternative form of prenylation which may reduce the efficacy of FTIs. Treatment of HGPS mice with statins and bisphosphonates inhibits both farnesylation and geranylgeranylation and improves nuclear shape (Figure 4a, 4c). The utilization of statins and bisphosphonates resulted in reduced lipodystrophy, reduced hair loss, improved bone defects, and enhanced longevity.[37] Pravastatin (a statin) and zoledronic acid (a bisphosphonate) are being studied in a second set of clinical trials as treatments for patients with HGPS. Pravastatin and zoledronic acid are commercially available in Canada and have been used in the prevention of cardiovascular disease and osteoporosis, respectively. A third set of trials has also been initiated in 2009 which examines FTI, pravastatin, and zoledronic acid in combination.[36]

HGPS GIVES INSIGHT INTO NORMAL AGING

Understanding HGPS and HGPS-related disorders (not discussed in this article) yields insight into general aging. Lamin A gene mutations exemplify the importance of the nuclear lamina in disease pathology to specific, but not all, tissues. For instance, brain function and development do not appear affected in HGPS, while cardiovascular, bone, fat, and skin pathology appear commonly. For affected tissues, it comes into question whether lamin A processing becomes awry during normal aging in unaffected individuals. Indeed, skin biopsies from elderly individuals exhibited prelamin A protein accumulation, while accumulation of prelamin A was less detected in young individuals.[38] This was despite translation of normal prelamin A that included the sequence required for Zmpste24 cleavage,[38] suggesting possible defects in Zmpste24 activity. Interestingly, vascular smooth muscle cells (VSMCs) from aged or artherosclerotic lesions also accumulated prelamin A.[39] It was revealed that prelamin A accumulation in VSMCs correlated with downregulated Zmpste24 mRNA levels. Therefore, it appears that lamin A misregulation, through a lack of or faulty post-translational modification, is associated with the normal aging process.

CONCLUSION

Despite being described in as early as 1886, it was not until this last decade that the precise cause of HGPS has been elucidated. Gene discovery paved the way for a greater understanding of HGPS, exploration of treatment options, as well as insight into the potential role of prelamin A in the general aging process.

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