Original Article

Hutchinson-Gilford Progeria Syndrome (HGPS) - Molecular Analysis Of Cause, Background And Treatment

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Abstract

HGPS, or "Hutchinson Gilford progeria syndrome," is a drastic rare genetic condition with extreme consequences. After birth, it causes premature and quick aging. By the presence of some type of symptoms and they are associated with aging, 'HGPS' is distinguished. Within the recent past in the 'LMNA gene', Individuals with HGPS have been shown to possess "de novo" point mutations, which denotes 2 important and major proteins and they spliced transcripts alternatively which bring about lamin A & C proteins. The role of lamins is very much relatable to the doorman of the genome itself and its contribution to disease is unimaginable. The most structurally important component of the nuclear envelope is class A lamins. It causes 11 different disease phenotypes, each with different severity and affected tissue. Here, we review mainly the features, inheritance, Lmna gene, and molecular genetics associated with HGPS. This noxious irremediable disease is the result of the silent alteration in the LMNA gene which makes a protein called "progerin". Patients with HGPS, most of them die in their teenage due to cardiovascular disease (CVD). Till date, there are no permanent ways out or medical or genetical therapies that upgrade or brush up the disease progression. Luckily Rapamycin has recently been revealed to be effective for not only removing faulty protein, it also inhibiting the geroconversion process, and a new technology is known as the CRISPR/Cas system has been developed that allows for permanent genome editing at specified loci.

Keywords : Lamins. HGPS. LMNA gene. Rare disease. DNA instability. Progeria.

1. INTRODUCTION

"Hutchinson Gilford progeria syndrome is", is a gene-related clutter or kind of disorganization, which is related to a characteristic like very early aging appearance. Originally it was described more than a hundred years ago (1886) when, A three years aged kid had a "congenital absence of hair and mammary glands with atrophic condition of the skin and its appendages," according to general practitioner Jonathan Hutchinson. It seemed like ectodermal dysplasia to him. Hutchinson noted a second case in 1895, but Hastings Gilford (1897) detailed him in much greater detail after following him for several years until his death at the age of seventeen [1, 2]. At the time of birth, Children with HGPS can appear healthy but within a year, they start unveiling characters of progeria syndrome. Some of the common traits are short and growth retardation, scalp veins, reduced size of the lower jaw, craniofacial inequality, baldness, large eye, and a lack of subcutaneous fat, which causes the skin to age and have normal intellect. Individuals have stiff joints and moderate limitations in motion as the condition progresses. The most common causes of death in 13-14 years of aging come about congestive heart failure [3, 4]. According to cytogenetic research, chromosome no-1 is the most probable contender chromosome for carrying the HGPS gene, and it was recently made known that progeria is triggered by lamin A gene alteration, (which is present on HSA1) [5,6]. The Lmna gene denotes two protein products lamin A and C, which is found on position 1q22. Lamin A, is a kind of inner nuclear lamina is involved in nuclear structure, chromatin alignment, and transcription, along with many other things [4, 7, 8]. Exon 11 of LMNA, which is positioned in this interval and has been linked to multiple other heritable illnesses, was shown to have a uniform denovo (not inherited & newly formed) single-base mutation, G608G (GGC>GGT). The codon 608 mutation is the most prevalent HGPS mutation. Exon 11 has a cryptic splice site as a result of this mutation, which obviates the need for a proteolysis domain in the altered lamin A that is expressed.

The HGPS mutation gives rise to the development of "Progerin," an altered protein of lamin A[7]. In a dominant-negative fashion, the accumulation of progerin disrupts the innermost nuclear membrane's structural stability. It's fascinating that distinct mutation sets in the 'Lmna gene, which specifies for proteins that interact with one another, such as emerin (EMD/STA gene) and BAF (barrier-to-autointegration, BANF1 gene), cause laminopathies [9, 10, 11]. Six separate recessive and dominant abnormalities are also linked with LMNA mutations, including Autosomal Emery Dreifuss muscular dystrophy, Dunnigan-type familial partial lipodystrophy, autosomal dominant limb-girdle muscular dystrophy 1B, and autosomal recessive axonal neuropathy [12, 13].

1.1 Inheritance

HGPS can be found in adjacent families and proposed as the rarest recessive disorder for observation of affected or problematic individuals [14-16]. However, numerous cases of progeria have been found in families whose parents are not associated with this disorder. More than half of a new heterozygous dominant mutation has been discovered in HGPS patients, in the 'LMNA' gene. Patients with apparent disabilities are very unlikely to be inherited from their parents because they cannot survive as long as they can reproduce[7] Others have proposed explanations for the occurrence of chromosomal abnormalities such as reverse insertion into chromosome 1 long arm [17], interstitial fruiting of chromosome 1q23[5], and frame transfer mutations. The importance of these cytogenetic signals in the finding of the HGPS gene has been proved.

1.2 Clinical features

Infants having HGPS appear normal at birth, but after a few years, they start to show signs related to quickened aging or maturation. Children encounter a delay in growth, short, and always stay below-average weight. Micrognathia or small jaw, craniofacial disproportion, alopecia or hair loss, prominent eyes, and veins showing on the scalp are the most common facial characteristics. Because of a lack of fat deposits, their skin appeared wrinkled and aged. Other notable features include tardy teeth, a riding horse attitude, a high-pitched voice, and a pyriform or pear-shaped thorax [18].

Musculoskeletal symptoms in HGPS, pear-shaped thoracic, debilitating and atrophic clavicle, narrow shoulders, limb arthrogryposis, flexion, and hip dislocation, "riding" (space between thighs). Most bones are susceptible to osteolysis and are at increased risk of hip dislocation and humerus fractures [19]. Thin lips, nasal bridge narrowing, lagophthalmos, and mandibular descent were notable features in the early days and also Cardiovascular problems appear within the first ten years of a person's existence and are a major cause of death. Secondary sexual characteristics are extremely uncommon, and breast development is almost non-existent. Calcified arterial lesions are the first sign of progressive vasculopathy, following that are vascular plaques, hypertension, angina, myocardial fibrosis, interstitial fibrosis, plus calcium deposits in various valves including the aortic and mitral valves [20]. Anodontia, hypodontia, malocclusion, tooth arrangement, prolonged prothrombin time, loss of earshot, hypertension, hyperphosphatemia, and elevated counts of platelet have all been observed [21].

For each year of their lives, the condition causes children to age by a decade. It represents respiratory, cardiovascular, and rheumatic disorders by the age of ten, just like a senior citizen [22]. In most cases, at the age of thirteen death takes place. 90% of HGPS patients die follows a result of growing atherosclerosis of the coronary and cerebrovascular arteries [23].

1.3 LMNA gene

LMNA genes are codes by Lamin (A & C) which is a structural protein element of lamin, located under the membrane of the inner core of the protein network and influences the nucleus' shape and size. Intermediate filaments are made up of a thin layer of fibrous. In mammalian cells, three forms of lamina have been identified: A, B, and C[24] Laminin C and A are estimated to have respectively molecular weights of 65 and 74 kD. The final amino acid sequence of lamella (human) A & C, cDNA clones is identical to the initial of 566 amino acids. However, at the C-terminal region, lamella A has an extra 98 amino acids (equal to roughly 9 kD) and lamin C has six distinct amino acids. laminin A & C both have a spiral domain with 360 residues that are structurally similar to the homologous-helical rod domain found in all intermediate filament proteins. As a result, Alternate splicing with the same gene produces laminin A and C [24, 25].

1.4 Relation between Aging and Progeria

Aging and progeria are related, due to the relationship between aging rate and telomere length [26]. TTAGGGs are telomeres, which are repeating sequences that wrap around each chromosome and shorten with each replication. Telomeres have a set length when they divide, and when that particular location is reached, the cell stops dividing and becomes old. In Progeria patients, extremely short telomeres are seen in test results. The aging of the skin and muscles, cardiovascular cells, and the central nervous system is associated with a decrease in telomeres. Repairing damaged DNA induces Progeria, as well as other diseases with accelerated aging. It is an autosomal recessive disorder [27]. Defect genes inherited by multiple genome maintenance mechanisms accelerate tissue-specific aging, including neurodegeneration.

1.4.1 Causes of HGPS

There is an opinion that LMNA is involved in some genetic diseases. G608G (GGC> GGT), E145K (GAG> AAG), and G608S (GGC> AGC) are the three forms of LMNA de novo mutations identified. The most common automatic mutation is G608G. A study conducted by Nicolas Levy revealed the same unique heterozygous C>T base mutation in the LMNA codon 608 in progeria patients [4]. Other homozygous and heterozygous alterations associated with progeria comprise

A57P, T528M, L140R, R527C, E145K, R644C, R471C, K542N, G608S, M540T, R133L, and T623S [6, 27, 31]. The basic unit of the nuclear membrane is Lamin A, which is scrap. It can occur as a parent's spouse or at the time of in a newly formed cell division in a pregnant or accepted mother. It is not usually notified to the sibling of the child who is caught. Multiple children in a single household can succumb to Progeria in rare situations [32]. When cells from progeria patients, elderly people, and young subjects were compared, they found that elderly cells & progeria patients had higher levels of DNA damage, histone proteins demethylation, and down-regulation of certain nuclear proteins [33].

1.4.2 Genetics related to the HGPS

It is reported that the denovo point mutation of Lamin A is the leading source of Hutchinson-Gilford syndrome [7]. Two examples of uniparental isodisomy of 1q and one case of paternal interstitial deletion of 6 mb were studied, researchers discovered that the HGPS gene was largely localized on chromosome 1q. 18 of the 20 classic HGPS cases resulted in a shift from gly to gly, which is automatic at codon 608 of exon 11 (G608G), as well as a C to T conversion. The activation of exon 11 of the lamin's cryptic binding site has been disclosed as a result of these variants. It allows for the creation of a protein with fifty amino acids removed near the C terminal region. Antibodies directed against lamin A were used to immunofluorescence HGPS fibroblasts, which indicated that many of the cells had obvious nucleus membrane defects[7]. In HGPS cells, alterations in the LMNA gene cause changes in group dynamics, DNA replication, RNA repair, transcription, and protein expression. The collection of "progerin" and the loss of lamin A get these three types of changes. This (i) Loss of nuclear structure and integrity is most important for the expression of abnormal genes and chromatin structures. (ii) Increase cell turnover due to increased cell death and division and (iii) Due to progerin's significant negative effect and the aberrant seizure of essential recovery proteins, DNA damage occurs. By this grown lamin A can target such proteins. The main function of lamin in HGPS has not yet been clarified, but functional outcomes may vary depending on the quality at which the multiprotein complex is attached to hexyl or points within the nuclear exodermis [34].

1.4.3 Molecular Background

HGPS is classified as a laminopathy and is also familiar as systemic laminopathies. A team from the 'National Human Genome Research Institute' in Maryland found the LMNA gene of progeria with other 80 different known genes, on a 4.82 Mb area of 1q chromosome [35]. A&B types of lamins make up an inner subcaste of the nuclear envelope. These lamins are important nuclear lamella protein factors. Defects in B-type lamin are deadly because they are involved in gastrulation and development, whereas in A-type of lamin cause laminopathies. Lamin A is a 664-amino-acid protein, that is usually made from prelamin-A which is a precursor molecule and has a cysteine aliphatic amino acid box (CAAX box) motif at the terminal-C region. In the end, this precursor patch prelamin- A is proteolytically split into two different pathways, one is at the C terminal, where tripeptide aaX is released enzymatically and then Methyl transferase adds a methyl group to the remaining farnesylcysteine [36]. The disposition of endpoints of 15 amino acids present on prelamin-A by zinc metalloproteinase forms mature lamin in the last phase [37]. Nuclear lamins regulate DNA synthesis and shape, gene expression, and chromatin association [38]. In mature A-type lamin, there is no revision of the farnesyl group. Because it is an extension of zinc metallopeptidase, is inhibited by STE24 (Zmpste24) gene absence, prelamin-A is produced. In exon 11 and position 1824, about 90% of HGPS instances had a single point mutation converting cytosine to thymine (GGC to GGT) [4]. This heterozygous single nucleotide mutation results in a patch that is 150 base dyads shorter than expected. The 50 amino acids that aren't restated contain Zmpste24 cleavage sites. Prelamin-A is farnesylated (keeping the 'CAAX motif') and affixed to an innermost subcaste of the nuclear envelope, resulting in the mutant protein " progerin". Because the progerin's prenyl group is linked to the nuclear envelope, the alternate cleavage point is missing. The nucleus of progeria patients is swelled and deformed, with a thick nuclear A-type lamin [39].

1.5 Molecular diagnostics

The mutant screening is hypothetically possible since the majority of HGPSs have the same denovo alteration at the same codon (G608G). The cost of studying genomic DNA, in particular, is minimized. Predictive screening is currently not achievable for currently available data due to the phenotype's sporadic nature. Therefore, there is no opportunity to identify if some children are in danger. Because there is presently no cure for progeria, the benefits are limited. The parent of a child who was previously afflicted, children may have a theory of parental somatic mosaic attention procedures or processes. Individual genetic testing may be helpful in association with the recurrence of HGPS in future pregnancies [5, 6]. LMNA genetic testing can also be useful for molecular diagnostics in individuals with implicit phenotypes, confirming that the disease is "classical" HGPS or those atypical pros are Lloyds. Is to do. Accurate molecular diagnostics are important in the current situation, as future treatments for progeria, as mentioned above, knowing the genetic basis of the trait may be necessary.

1.6 Treatment

To remedy the abnormalities in progeria, a variety of therapy techniques have been proposed: (i) Direct "repair" of the disease-causing mutation; (ii) For preventing progerin mRNA synthesis by suppressing pre-mRNA aberrant splicing; (iii) reducing the toxicity of progerin that has been isoprenylated and methylation; (iv) for the purpose of causing progerin clearance; (v) For reducing the unpleasant downstream consequences associated with progerin accumulation.

1.6.1 PrelaminA, Isoprenylation, and methylation inhibitors

Progerin is made when the ZMPSTE24 cleavage site is lost, which is normally used to eliminate the farnesylated carboxy-terminus from prelamin A during post-translational processing. Monoaminopyrimidines and isoprenylcysteine carboxyl

methyltransferase inhibitors, such as lonafarnib, Zoledronate, or Pravastatin, are used to remove the farnesylated carboxy. Isoprenylation was another result of inappropriate post-translational modification of prelamin A in progeria [40, 41].

1.6.2 Mouse model study: In a mouse model research, inhibiting the NF-B pathway boosted body weight and lengthened lifespan. The spleen returned to normal lymphoid status after therapy. The tissue bulk, cellularity, and architecture of the thymus were all normal [42]. Silencing the HGPS mutation therapy, which included osteocyte and osteoblast-specific inducible transgenic expression of the HGPS mutant, produced considerable results by normalizing bone shape and mineralization. So the number of osteocytes in the rebuilt bone has grown [43]. Another investigation in mice demonstrated that preventing pathogenic Lmna splicing lowered progerin accumulation, improved progeroid characteristics, and increased lifespan [44].

1.6.3 Farnesyl Transferase Inhibitors (FTIs), Statins and Aminobisphosphonates

The main goal for this remedy is to reduce energy demand while increasing the height and weight of HGPS cases. The pharmaceutical reclamation system was put in place, which uses FTIs that were originally created as chemotherapeutic agents. FTIs were discovered to reduce the disease's inflexibility, according to the findings of preclinical investigations. These drugs work primarily by preventing progerin from becoming farnesylated and thereby slowing disease development. All posterior processing responses are suppressed by FTIs, which inhibit FPT (farnesyl protein transferase) and regulate farnesylation of prelamin-A with the CAAX motif at the C-terminus. FTIs assist prevent the beginning of the cardiovascular disease and postponing its progression [45]. Failures to respond to lonafarnib treatment included inhibiting of B1 & B2 lamin farnesylation and it's possible that more serious damage to the nuclear lamella will occur. In the absence of farnesyl protein transferase, Geranylgeranylation is an alternate process of prenylation that recycles prelamin-A. As a result, progerin levels rise, lowering the efficacy of FTIs in treatment. Statins and amino bisphosphonates can prevent this revision by suppressing the product of both geranyl-geranyl and farnesyl precursors (Fig 1). This finding explains why in a mouse model, FTI therapy just enhanced lifespan and it has evoked a number of ongoing corrective treatments. FTIs are mixed with statins, like pravastatin, and amino bisphosphonates, such as zoledronic acid, in these clinical trials, which has proven to be a significant ongoing technique for improving disease treatment [46].

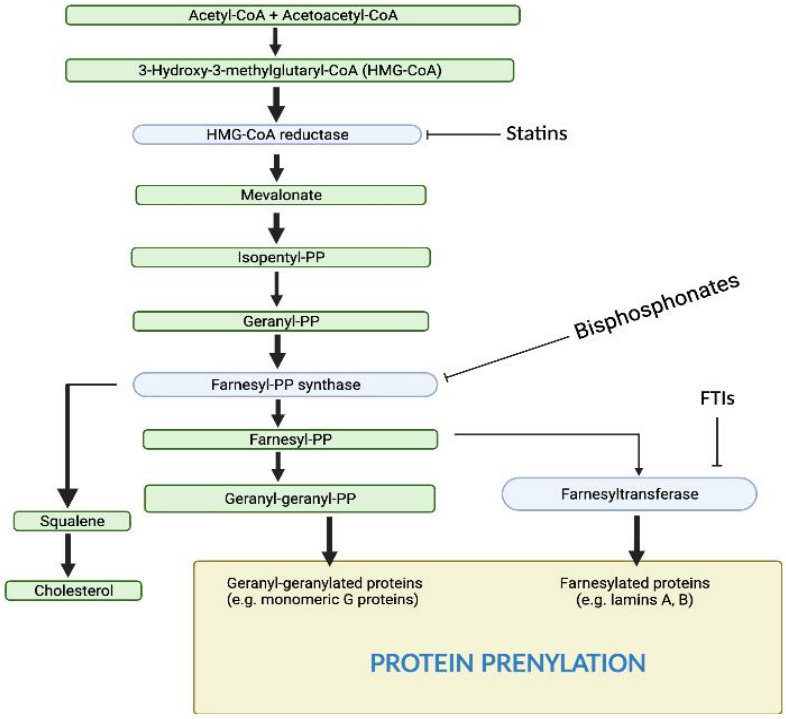

Fig. 1: Mode of action of Statins and FTIs in HGPS through the isoprenoids and cholesterol biosynthesis. PP means Pyrophosphate

1.7 Rapamycin

Rapamycin is an immunosuppressive medication used to prevent organ rejection after transplantation, promotes autophagy-induced progerin clearance, improves abnormal nuclear morphology, and delays the appearance of aged HGPS fibroblasts [47, 48]. It acts by removing progerin, which slows senescence and extends the lifespan of affected cells by preventing the creation of structural defects in the nucleus. It also acts by delaying the onset of atherosclerosis and the ageing process. Protein synthesis, cell proliferation, osteoclast reorganization, transcription, immunological or autonomous responses are all known to be regulated by this protein. Therefore, great care must be taken when converting the results directly into children's test tubes who is affected by progeria. Rapamycin is also known to suppress the production of fat tissue [49, 50], As a result, when utilizing this medication in HGPS patients with systemic atrophy and lipodystrophy, precaution should be exercised.

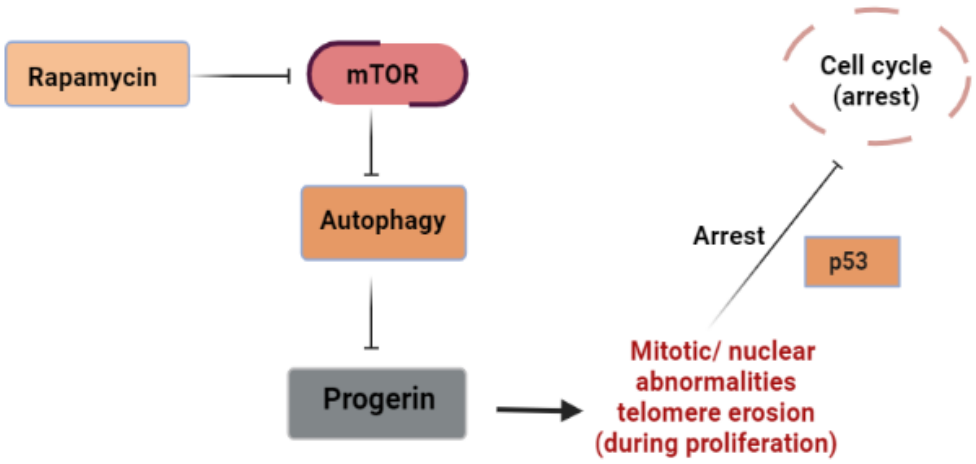

Fig. 2: Mode of action of Rapamycin in HGPS treatment

1.7.1 Sulforaphane

Sulforaphane, a cruciferous vegetable-derived antioxidant, has similarly been shown to improve autophagy-induced progerin clearance and reverse the cellular characteristics of HGPS in vitro. Scientists have determined that MG132 is effective in breaking down progerin. MG132 induces a progerin translocation in the cytoplasm after transformation. Through nucleolar progerin clearance and macroautophagy in fibroblasts and induced pluripotent stem cells-derived mesenchymal stem cells (MSC) and vascular smooth muscle cells (MSC) in HGPS patients. With In vivo progerin expression was reduced in the skeletal muscle of Lmna (G609G / G609G) mice treated with MG132 in HGPS fibroblasts [5, 7].

1.7.2 Gene therapy

Research data show that intravenous injection of a single dose of CRISPR-Cas9- into a Lamin A/progerin sample where HGPS mice's health was enhanced, and their longevity was extended. In this study, transformed mice were used to provide expressed S. pyogenes Cas9 and gRNAs demonstrating exogenous concepts. By demonstrating similar human processes / experiments that divert the intraperitoneal transmission Cas9 and gRNA of *Staphylococcus aureus* [33].

1.7.3 RNA Therapy

HGPS is caused by the activation of an alternative pre-mRNA splice site. In 2005, Scaffidi and Misteli demonstrated that antisense oligonucleotides inhibited HGPS fibroblasts' pre-mRNA splice site [51]. Antisense oligonucleotides were also found to reduce the accumulation of defective protein progerin and its associated abnormalities, such as decreased life span, in a new HGPS mouse model constructed in 2011 based on symptoms of real HGPS patients [44]. It was further supported by the fact that the HGPS mouse model gained weight and lived longer [52], where small interfering RNA (siRNA)-based approaches were used to exclude the progerin mRNA, which was a necessary step.

1.7.4 Stem Cell Treatment

Somatic cells derived from human induced pluripotent stem cells (iPSCs) have been found to develop an in-vitro HGPS disease model, due to better reprogramming technology. HGPS changes will be caused by stem cell dysfunction. Progerin inhibits human mesenchymal stem cell development and multipotency in vitro, and HGPS patient-derived iPSCs show abnormalities in differentiation [53]. In an HGPS-related cellular model, epidermal stem cell proliferation efficiency was lowered. In 2011, Zhang et al produced brain cell lineage from iPSCs collected from HGPS patients in order to assess laminA expression in these cells [54]. Nissan et al. proposed the pathogenic relationship between mi-R9 and brain cells for the first time. They discovered that brain cells with low mi-R9 expression were protected from accumulation induced cell defects of progerin [55]. Mesodermal stem cells (MSCs) generated from HGPS patients' iPSCs to demonstrate progeria-related defects [56, 57]. Treatment of MSCs with three different medication classes, namely FTIs, rapamycin, and a combination of pravastatin and zoledronate, alleviated all cellular abnormalities associated with progeria. As a result, iPSC-derived cells are the most effective way to assess disease pathophysiology, therapeutic action mechanism, and compare the effects of different combinations of the drug.

1.7.5 Conclusion

Because progeria is such a rare disease, current research and data are insufficient to fully comprehend the disease's characteristics and to provide the most effective treatment or complete eradication. There is no cure based on current data. Regularly monitoring patients and genetic counseling can help children reduce cardiovascular disease. Other treatments, such as high-calorie diet-related supplements that can help you lose weight and low-dose heart disease desires, can help you manage your symptoms. The finding of HGPS mutations results in a total of 9 disorders caused by the mutant LMNA, emphasizing the vast spectrum. Future studies on HGPS may reveal vital insights into the aging process and aging-related disorders.

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CONFLICT OF INTEREST

There is no conflict of interest

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