Review Article

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Progeria: A rare genetic premature ageing disorder

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Progeria is characterized by clinical features that mimic premature ageing. Although the mutation responsible for this syndrome has been deciphered, the mechanism of its action remains elusive. Progeria research has gained momentum particularly in the last two decades because of the possibility of revealing evidences about the ageing process in normal and other pathophysiological conditions. Various experimental models, both *in vivo* and *in vitro*, have been developed in an effort to understand the cellular and molecular basis of a number of clinically heterogeneous rare genetic disorders that come under the umbrella of progeroid syndromes (PSs). As per the latest clinical trial reports, Lonafarnib, a farnesyltranferase inhibitor, is a potent 'drug of hope' for Hutchinson-Gilford progeria syndrome (HGPS) and has been successful in facilitating weight gain and improving cardiovascular and skeletal pathologies in progeroid children. This can be considered as the dawn of a new era in progeria research and thus, an apt time to review the research developments in this area highlighting the molecular aspects, experimental models, promising drugs in trial and their implications to gain a better understanding of PSs.

Key words Accelerated ageing - clinical trial - experimental models - farnesylation - Hutchinson-Gilford progeria syndrome - lamin A - *LMNA* gene - lonafarnib - longevity

Introduction

Progeroid syndromes (PSs) are a group of fatal, severe and rare genetic disorders characterized by various clinical features and phenotypes of physiological ageing prematurely. These syndromes include clinically and genetically heterogeneous diseases such as ataxia-telangiectasia, Bloom syndrome, Cockayne syndrome, Fanconi anaemia, Hutchinson-Gilford syndrome, Rothmund-Thomson syndrome, trichothiodystrophy, xeroderma pigmentosum, and Werner syndrome (also known as adult progeria)[1]. Among the different forms of progeria, the classical and most extensively studied type is the Hutchinson–Gilford progeria syndrome (HGPS), named after the two scientists (Jonathan Hutchinson in 1886 and Hastings Gilford in 1897) who independently delineated and described the syndrome.

Epidemiology, prevalence and common symptoms of HGPS

As of now, the prevalence of this syndrome is one in 4 - 8 million new births[2] . Incidence of progeria is uniform throughout the world showing no gender, geographical or ethnic predisposition, and hence

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mostly considered as sporadic. Presently, there are about 114 children across 39 countries diagnosed with HGPS[2]. The average age of survival is 13.5 years (with life expectancy about 8 - 21 years) and death occurs due to stroke, myocardial infarction[3], heart failure or atherosclerosis (cardiovascular disease). Of the clinical symptoms of various PSs like growth retardation, skin atrophy, alopecia, lipodystrophy, osteolysis and an augmented susceptibility for malignant tumours, the notable thing in HGPS is that the cognitive abilities remain unaffected[4,5].

Classical HGPS is usually caused by a sporadic autosomal dominant mutation (except unique inheritable variety such as Werner's syndrome)[6]. There are a few atypical forms of progeria, also called non-classical progeria in which growth is less retarded, scalp hair fall off slowly, progression of lipodystrophy is delayed, osteolysis is more visible with exception in face and survival is observed mostly till adulthood[4]. Non-classical HGPS follows autosomal recessive pattern of inheritance[4]. Mostly, HGPS occurs as a result of a *de novo* point mutation in the DNA[7] . These children look normal and healthy at birth but in due course of time (mostly within a year) they gain very less weight due to growth failure. By the age of one and a half to two years, they are thin with small face and abnormal jaw size relative to the size of head, have high-pitched voice, irregular dentition, a pinched nose and notably big wide-open eyes, undersized dystrophic clavicles and absence of sexual maturation[8]. Body fat and eyelashes are progressively lost and hair start becoming thinner and fall off, finally to become completely bald (alopecia). The skin becomes very thin, delicate and translucent through which veins could be seen[8]. Complaints of angina, high blood pressure, stiffness of joints and hip dislocation are also common. Clinical findings show that these patients show prolonged prothrombin time and elevated platelet count which is not seen in normal physiological ageing[9]. The biochemical analyses show normal results except for the increased low-density lipoproteins and cholesterol levels in the serum and increased urinary excretion of hyaluronic acid (HA) in these patients[10].

As an estimate, these children biologically age about ten years in a single year. One remarkable thing is that they have normal IQ and intelligence. Till date, not many studies have been done to evaluate various signaling pathways or neurochemical profile in the brain of such subjects. Therefore, the involvement of brain signaling pathways in the pathogenesis of the disease cannot be ruled out. Advancement of heart disease occurs at an exceptionally accelerated rate in these children at the age of around 13 years which is comparable to the prevalence in normal population around the sixth decade or so[2]. Only a single report of the survival of a patient up to 45 years has been reported[11].

Other progeroid syndromes

Werner syndrome (WS) is a rare PS very similar to HGPS in its clinical symptoms. It is inherited as an autosomal recessive trait. The mutation lies in the *WRN* gene encoding DNA helicase, located on chromosome 8, which impairs telomere maintenance and further DNA replication in the cell. Individuals with this syndrome develop normally until about 10 years of age and exhibit clinical symptoms in early teenage years. The mean age of survival in WS is 54 years[12,13] . WS is more prevalent in Japan and in the Italian island of Sardinia than any other part of the world. About 1000 cases are reported in the world; more than 800 of these cases are in Japan[14,15]. There is another similar and rare premature ageing syndrome known as dyskeratosis congenita (DKC). DKC is an inheritable bone-marrow failure disorder linked to mutations in *DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TIN2* or *TCAB1* genes[16], implicating the physiology of telomeres[17].

Trichothiodystrophy (or Tay's syndrome) is an autosomal recessive disease identified by small stature, mental and overall growth retardation, ocular defects, brittle hair and other developmental abnormalities like congenital ichthyosiform erythroderma. Patients have abnormal production of transcription factor II H (TFIIH), a general transcription factor active in basal transcription and nucleotide excision repair, due to mutations in genes encoding any of the 3 subunits of TFIIH—*ERCC2 (XPD), ERCC3 (XPB*), and *GTF2H5 (TTDA*)[18].

Cockayne syndrome, another rare congenital disorder, is characterized by growth failure, atypical photosensitivity and importantly impaired development of the nervous system. Mutations in any of the *ERCC6* and *ERCC8* genes bring about defect in DNA repair mechanism which eventually precipitates this disease[19]. By the age of two years, growth and development of the individual becomes abnormal. The distinctive physical appearance of cachectic dwarfism with sunken eyes, reduction of the skin and hair thickness and an arched standing posture characterizes the ageing process. Neuropathological investigations

demonstrate widespread demyelination in the central and peripheral nervous systems of the patients. There is also neuronal loss in the cerebral cortex and cerebellum, and calcification around capillaries in the cerebral cortex and basal ganglia[1]. These children show cognitive impairment and intellectual deficits which often worsen with age[20]. A summary of different PSs with their clinical symptoms has been illustrated in Table.

Molecular aspects

The two known molecular lesions of HGPS are the mutated *LMNA* gene and/or abnormal post-translational processing (*ZMPSTE24* gene mutations) both of which ultimately result in abnormally formed lamin A called progerin. *De novo* point mutations in the lamin A/C gene called *LMNA* (which produces lamin A and lamin C proteins as alternative splice products) causes HGPS[7,21]. Most of the HGPS cases (around 90%) carry the LMNA G608G (GGC>GGT) mutation within exon 11 of *LMNA* which activates a splice donor site that results in production of a dominant negative form of the lamin A protein[22]. *LMNA* gene is present on chromosome 1 and the point mutation results in the deletion of 50 amino acids of prelamin A[23] which destabilizes the nucleus further and is fatal for the cell. Cells with abnormal nuclear shape are often implicated in a number of disease pathologies in which lamin A proteins are mutated, collectively referred to as laminopathies[24]. Lamin A is a key protein component of nuclear scaffolding that holds the nucleus together by forming the inner layer of the membrane. Due to its deficiency, the young patients of HGPS develop various phenotypic characteristics like loss of hair, development of craniofacial deformities, wrinkled appearance and cardiovascular defects leading to heart attack or stroke. The disease is characterized by definite defects in nuclear shape due to the mutated gene resulting in distorted nuclear membranes in 50 per cent of the cells as compared to less than 1 per cent cells of the normal individuals[25]. Ageing related distortion in nuclear shape in humans is also known to be linked to the nuclear lamina, particularly to progerin, as seen in cases of HGPS[25]. Interestingly, brain, unlike other tissues, predominantly synthesizes lamin C and very little prelamin A and thus escapes the deleterious effects of *LMNA* mutation. This probably explains why HGPS patients are spared from any pathology related to brain[26].

Cells expressing mutant lamin A show aberrant DNA damage responses[27] and since lamin A expression is restricted to a few cell types there is an explicit difference in the cells and tissues getting affected. Further, as the defective lamin A protein makes the nucleus unstable, the resultant cellular instability appears to lead to the process of premature ageing in progeria. *In vitro* studies employing a morpholino oligonucleotide targeted to the activated cryptic splice site showed the reversibility of the diseased cellular phenotype by correcting the aberrant splicing episode. However, there was no rescue from the symptoms by simply introducing the wild-type lamin A protein[28]. Interestingly after the splicing correction,

Table. Summary of gene mutations leading to various progeroid syndromes with their clinical symptoms

Syndrome	Mutation in gene	Clinical symptoms
Hutchinson-Gilford progeria syndrome	*LMNA*[3-5]	Growth retardation mostly evident within a year of birth, skin atrophy, alopecia, osteolysis, cardiovascular complications, *etc*.
Werner's syndrome	*WRN*[12]	Symptoms appear mostly during early teenage years; development of cataract, atherosclerosis, skin atrophy, osteoporosis, *etc*.
Trichothiodystrophy or Tay's syndrome	*ERCC2, ERCC3* or *GTF2H5*[18]	Growth and mental retardation, congenital ichthyosiform erythroderma, brittle hair.
Cockayne's syndrome	*ERCC6; ERCC8*[19]	Growth failure, atypical photosensitivity, impaired development of the nervous system, poor cognitive skills, loss of hearing and visual abilities, *etc*.
Dyskeratosis congenita	*DKC1, TERC, TERT, NOP10, NHP2, TIN2* or *TCAB1*[16]	Nail dystrophy, abnormal skin pigmentation, mucosal leukoplakia and pulmonary complications.

Source: Refs 3-5,12,16,18,19

the HGPS cells show normal nuclear morphology with corrections in aberrant cellular levels and distribution of lamina-associated protein and also the rectification of the errors in heterochromatin-specific histone modifications[28]. Other disorders like Emery-Dreifus muscular dystrophy, atypical Werner syndrome and Charcot-Marie-Tooth type 2B1, in addition to HGPS, can occur due to mutations in the *LMNA* gene[29-31] .

The post-translational processing of prelamin A has been thoroughly illustrated[32]. The farnesylation of a C-terminal cysteine (the C of the CAAX motif), endoproteolytic release of the last three amino acids (the AAX) and methylation of the newly exposed farnesylcysteine residue are involved in the process triggered by prelamin A. Further, ZMPSTE24 (an endoplasmic reticulum membrane protease) cleaves prelamin A at the C terminus including the farnesylcysteine methyl ester to release a total of 15 more residues to generate the full lamin A. On the other hand, progerin has been shown to provoke various progerian phenotypes in mice irrespective of being farnesylated or not[33]. Lamins are known to interact with various inner nuclear membrane proteins of which the SUN domain protein called SUN1 has been implicated in the pathogenesis of HGPS. Chen *et al*[34] have reported that loss of *Sun1* gene in *Lmna*$^{-/-}$ mice corrects the cellular and tissue related abnormalities and remarkably improves lifespan. Also, by knocking down over accumulated SUN1 from primary HGPS cells, they showed that problems like nuclear defects and early cellular senescence got corrected. Over accumulation of SUN1 is considered to play a key role in HGPS and hence holds a promise in designing therapeutic strategies in future.

Various hypotheses have been put forward for the involvement of reactive oxygen species, oxidative stress and defects in the DNA repair mechanism to explain their roles in the accelerated ageing process in the HGPS condition[1]. Telomeres have been observed to be involved in various PSs including HGPS. It has been reported that telomere length is shorter in HGPS fibroblasts compared to age-matched controls[35]. Another study suggests that mutant lamin A reduces telomere length through a direct effect and that expression of mutant LMNA is a requisite for telomere loss in HGPS[36]. The increased cell death in an organism can be due to some aberration in DNA repair mechanism or shortening of telomere or defects in telomeric DNA. It may be due to either or any combination of these reasons[37].

Experimental models of progeria

In order to develop a better understanding of the pathogenesis and progression of PSs and design potential therapies, effort has been put in by scientists globally to develop animal models of the same. *Lmna*$^{-/-}$ mice develop cardiac and skeletal myopathic phenotype similar to the Emery-Dreifuss muscular dystrophy in humans[38]. Another study showed that homozygous mice carrying autosomal recessive mutation in *Lmna* gene have a phenotype resembling HGPS, with marked growth retardation, pathologies of skin and bone and death by 4-5 weeks of age[39]. DNA repair deficient *Ercc1*$^{-/-}$ mice show a slight retardation in embryonic and early post-natal development, but the growth almost stops in the second post-natal week, leading to death by 4 weeks of age[40]. These *Ercc1*$^{-/-}$ mice exhibit skin, liver and bone marrow pathologies, progressive ataxia and premature ageing. *Zmpste24*$^{-/-}$ mice are normal at birth but soon develop progeroid symptoms like alopecia, kyphosis, abnormalities in dentition and bones, *etc*[41,42] which improve when treated with protein farnesyltransferase inhibitor (FTI)[43,44]. *Zmpste24*$^{-/-}$ mice also exhibit very high circulating levels of growth hormone (GH) and a drastic reduction in plasma insulin-like growth factor 1 (IGF-1)[45]. The GH/IGF-1 signaling is known to be crucial for the control of longevity[46]. Recombinant IGF-1 treatment refurbishes the balance between IGF-1 and GH in *Zmpste24*$^{-/-}$ mice, delays the onset of many progeroid symptoms and improves their lifespan considerably[45]. *In vitro* studies also implicate the possible role of FTIs in the treatment of HGPS[47]. A recent study has shown that rapamycin inhibits aberrant mTORC1 signaling in *Lmna*$^{-/-}$ mice and improves their cardiac and skeletal muscle functions thereby enhancing their survival[48].

Current status of diagnosis, drugs and medication

Although the pursuit for finding an effective treatment for HGPS is still on, yet there is still no diagnostic kit available for early detection of the same. Usually in practice, a clinical assessment is done based on the phenotypical evidence and medical history of the child. Following this, a genetic test for *LMNA* mutation is commonly done for confirming the diagnosis of HGPS to initiate the treatment programmes early in the progression of the disorder. A case report on HGPS has reported that clinical diagnosis can also be established by radiological findings - diastasis of the sagittal suture with several wormian bones in the skull; hypoplastic mandible with infantile angle; the presence of fish-

mouth vertebrae; the occurrence of bilateral coxa valga deformity; resorption of terminal phalanges, *etc*[10].

A class of cancer drugs known as farnesyltransferase inhibitors (FTIs) has shown promise of reversing the structural abnormalities of the nucleus (associated with build up of prelamin A) which is one of the characteristics of the cells in the HGPS children. As the name suggests, these drugs restrict the activity of farnesyltransferase required to make a liaison between farnesyl groups and progerin proteins. FTIs have shown improvement in many of the features of progeria-like mouse model[33,49]. Specifically, FTIs improve the nuclear shape in the fibroblasts from the patients of PSs[50] and improve nuclear blebbing in the fibroblasts of mouse model with the gene targeted for HGPS[23]. One study has shown the prevention of both the onset and late progression of cardiovascular disease by a FTI (Tipifarnib) in a transgenic *LMNA* G608G mouse model of HGPS[51] supporting the use of these drugs. Varela and co-workers[52] have shown prelamin A and its truncated form progerin/LADelta50 to undergo alternative prenylation by geranylgeranyltranferase when the farnesyltransferase was inhibited. This study has tried to explain the low efficiency of FTIs in improving the physical composition of the progeroid mouse models. They further showed that the combination of statins and aminobisphosphonates inhibited both farnesylation and geranylgeranylation of progerin and prelamin A and also improved ageing related phenotype of *Zmpste24*$^{-/-}$ mice strikingly. In addition, these extended the longevity of the mice significantly[52].

Under the partnership of Progeria Research Foundation, National Institutes of Health, Children's Hospital Boston and Dana-Farber Cancer Institute, the progeria clinical drug trial was initiated in 2010 to test the effectiveness of three 'drugs of hope' – a statin drug called Pravastatin (normally used for lowering cholesterol and preventing cardiovascular disease), a bisphosphonate drug called Zoledronic acid (usually used for improving osteoporosis and to prevent skeletal fractures) and a farnesyltransferase inhibitor called Lonafarnib (a drug that reversed progeroid associated phenotype and abnormalities in various murine models)[53]. The clinical trial conducted in 25 progeroid children over two years has reported that Lonafarnib, a FTI drug, has been successful in facilitating weight gain and improving cardiovascular and skeletal pathologies[54]. This is a tremendous achievement in the progress of progeria research that will perhaps pave its way to the discovery of a definite treatment for this rare and complex syndrome.

Scope for future research

Progeria (or HGPS) is a rare syndrome which makes it difficult to study. Due to the efforts of parents of the affected children, a few research groups and the Progeria Research Foundation (PRF), the awareness of this syndrome has increased significantly. Research has also proposed probable markers for this syndrome. For example, elevated HA levels have been suggested as specific marker for HGPS[10,55,56] , but other studies have nullified this by reporting that urinary and serum levels of HA in HGPS patients are comparable with controls[57]. Gordon and co-workers[57] did a thorough analysis of the serum and urinary hyaluronidases by both quantitative (using ELISA) and qualitative (using a gel detection method) methods and contravened the use of HA as a marker for HGPS. Hence, the search for an accessible and definite kind of diagnostic marker is still on.

The role of GH/IGF-1 axis in determining longevity has long been known[58]. A study has shown that DNA damage results in suppression of the GH/IGF-1 axis which in turn leads to remarkable progeroid symptoms[40]. More research on the causes and patterns of DNA damage in HGPS and ageing may provide some useful links between ageing and PS(s). The positive or negative interactions between the *LMNA* gene and other genes controlling ageing and longevity can be studied in appropriate animal models for better understanding of the pathogenesis and progression of HGPS. The PRF has 121 cell lines in their Cell and Tissue Bank, which are available on request for research purposes. A clear perception of the mechanism of pathogenesis of HGPS and other PSs would be helpful in understanding the abnormal conditions in the diverse branches of basic and applied life sciences like molecular biology, basic cellular senescence phenomenon, mitochondrial physiology, oncology, functional genomics and proteomics, dermatology especially dermal physiology, stem-cell biology, and many other degenerative disorders regarding which our knowledge is still meager[59]. Thus, discovery of a cure for PS(s) would not only help the affected children but also a large number of patients suffering from cardiovascular diseases, stroke, cancer, *etc*.

Proteins linked to HGPS are suspected to play a pivotal role in the ageing process and this could be one of the reasons responsible for making these children

predisposed to premature, progressive heart disease. When factors like IGF-1 signaling and functional cascade of events (of hormones) are checked in the prevalent and existing models of ageing and longevity (diet restriction), it has been observed that there is a significant shift from the normal parameters. This shift can be due to pituitary or any organ related faults, defect in the micronutrient (like vitamin D, *etc*.) metabolism, abnormal protein glycation, disturbed antioxidant status, to any other physiological process. It has been observed that WNIN/Ob (Wistar of National Institute of Nutrition obese rat) obese rats exhibits an unusual premature aging[60], develop various tumours, and have other immune response deficits[61,62]. These kinds of animal models should be checked for their genomic, proteomic and biochemical status to look into the details of the common or shared and probably faulty pathways.

Conclusion

The field of gerontology gained importance relatively late when compared to other areas of research. However, presently a lot of effort is being put in by researchers in this area to delay the normal ageing process and the trauma that follows the common physical, psychological, and social implications associated with it. The inheritance pattern of HGPS is known but it appears mostly as a sporadic disorder. Hence to address it efficiently it will be worthwhile to study the causal cellular and molecular mechanisms that accelerate the ageing process leading to rapid progression of the disease.

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