Atherosclerosis and Cardiovascular Diseases in Progeroid Syndromes

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Hutchinson–Gilford Progeria Syndrome (HGPS) and Werner syndrome (WS) are two of the representative genetic progeroid syndromes and have been widely studied in the field of aging research. HGPS is a pediatric disease in which premature aging symptoms appear in early childhood, and death occurs at an average age of 14.5 years, mainly due to cardiovascular disease (CVD). Conversely, WS patients exhibit accelerated aging phenotypes after puberty and die in their 50s due to CVD and malignant tumors. Both diseases are models of human aging, leading to a better understanding of the aging-associated development of CVD. In this review, we discuss the pathogenesis and treatment of atherosclerotic diseases presented by both progeroid syndromes with the latest findings.

**Key words:** Hutchinson–Gilford progeria syndrome, Werner syndrome, Atherosclerosis, Cardiovascular disease, Aging

**Introduction**

In 2020, the world’s population aged 65 or older was 7.27 million. Over the next 30 years, the number of older people worldwide will be more than double and is projected to exceed 1.5 billion by 2050. Aging is an independent risk factor for the development of cardiovascular diseases (CVDs) and considered to be the greatest risk. Therefore, the research focused on the mechanism underlying aging-associated CVD development is essential.

Progeroid syndrome represented by Hutchinson–Gilford progeria syndrome (HGPS) and Werner syndrome (WS) has been studied as a model disease of human aging because aging-like symptoms appear from a young age and their pathological condition mimics general aging. These premature aging syndromes also display the early onset of CVD. This paper outlines the clinical features and molecular mechanisms of the two aforementioned syndromes, focusing on atherosclerotic diseases, with the latest findings.

**Hutchinson–Gilford Progeria Syndrome**

HGPS is an ultra-rare autosomal dominant genetic premature aging syndrome that occurs in one in four to eight million births and causes death at an average age of 14.5 years due to myocardial infarction or stroke. Because of the abnormal splicing of the LMNA gene on chromosome 1, the lamin A protein encoded by this gene cannot be normally produced, and an abnormal protein called progerin accumulates in the nucleus. The main symptoms are scleroderma-like skin, joint contractures, bone abnormalities, hair loss, growth retardation, and atherosclerotic diseases, such as myocardial infarction and stroke.

**Clinical Characteristics of HGPS**

Infants with HGPS are normal at birth, but the mean weight is slightly small for gestational age. The first pathognomonic signs are prominent veins on the nose bridge, followed by growth retardation, hair loss, and reduced subcutaneous fat around 6 to 12 months, and the diagnosis is often made between 2 and 3 years.
of age. Symptoms in the craniofacial region gradually appear, including alopecia, with only a few hairs, abnormally prominent scalp veins, larger skull than the facial bone, pseudo-protrusion of the eyes due to a decrease in surrounding adipose tissue, loss of subcutaneous fat and muscles in the face, a narrowing of the nose bridge and a hooked nose, wrinkles around the lips due to thinning of the skin, abnormal dentition, and carries, a small jaw, large ears lacking earlobes, and a high-pitched voice. Symptoms in the trunk and extremities include loss of subcutaneous fat and muscle mass, protruding joints and decreased range of motion, and hypertrophy of the tips of the fingers. On the other hand, there is no intellectual impairment or psychiatric symptoms, and most of the affected children are charming and active. The growth disturbance is remarkable, especially in weight, with most children over 12 years old weighing around 15 kg (same as 3- to 4-year-old healthy children). As a result, they gradually develop the appearance resembling older people.

In a report of 15 white patients (median age, 6 years and 11 months), the average body fat percentage was as low as 16% (below −1 SD) and tended to decrease with age. Seven had higher blood pressure than healthy children of the same age and height, five had abnormal electrocardiograms, and three had echocardiographic abnormalities at rest. Carotid artery ultrasonography revealed adventitial thickening in all patients and stenosis and occlusion in three. In addition, the ankle-brachial index decreased in three patients. Although muscle strength was preserved, 11 patients had osteoporosis, and all 15 patients had osteolysis of the distal phalanges and clavicles, as seen on X-ray. Blood tests revealed a decreased level of high-density lipoprotein cholesterol in 10 patients. Glycated hemoglobin was in the normal range, but five had elevated fasting insulin levels, and one was diagnosed with diabetes via oral glucose tolerance test. The creatinine and urea nitrogen levels were in the normal range.

The cause of death is predominantly CVD. CVD events do not occur until around the age of 5 years, but the children gradually suffer from dyspnea due to heart failure or ischemic heart disease and paralysis caused by stroke. Myocardial infarction and heart failure are frequent and account for 80% of deaths. Other reported causes of death include intracranial hemorrhage, seizures, infections, and complications from cardiovascular surgery.

In autopsy, the loss of vascular smooth muscle in the media is prominent. Calcification and plaque formation in the coronary arteries vary from patient to patient. A study that assessed 27 HGPS patients reported that diastolic dysfunction was the most prevalent cardiac abnormality. Other abnormalities, such as left ventricular (LV) hypertrophy, LV systolic

| Table 1. Summary of the characteristics of HGPS and WS |
|-----------------------------------------------|
| **HGPS** | **WS** |
| Disease prevalence | 1 in 20 million<sup>6</sup> | 9.0 in 1 million in Japan<sup>7</sup>, 1.0 to 2.7 in 1 million globally<sup>7</sup> |
| Ethnicity | Ubiquitous<sup>7</sup> | Relatively prevalent in Japanese and Sardinian<sup>7</sup> |
| Sex | Equally affected<sup>7</sup> | Equally affected<sup>8</sup> |
| Lifespan | Average 14.5 years<sup>6</sup> | Average 55.0 years<sup>65</sup>, median 54.3 years<sup>88</sup> |
| Responsible gene and frequent mutation | LMNA: c.1824C>T (90% of patients)<sup>7</sup> | WRN: c.3139-1G>C (70.7% of allele in Japanese patients), WRN: c.1105C>T (18.6% of allele in non-Japanese patients)<sup>7</sup> |
| Diabetes or IGT | 15.4% of patients<sup>6</sup> | 67.5% of patients<sup>67</sup> |
| Dyslipidemia | 71.4% of patients<sup>6</sup> | 65.0 to 85.0% of patients<sup>52, 67</sup> |
| Hypertension | 46.7% of patients<sup>6</sup> | 42.5% of patients<sup>67</sup> |
| CVD | 100% had adventitial thickening in the carotid artery, 18.2% had the low ankle-brachial index<sup>6</sup> | 15% had ASO, 2.5% had AP or MI, none had cerebral artery disease<sup>7</sup> |
| Causes of death (percentage of total) | Heart failure (80%), head injury (9%), complications of surgery (4%), stroke (3)<sup>7</sup> | Malignancy (56%), AMI (28%), infection (14%), cerebral bleeding (2)<sup>65</sup> |

Abbreviations: IGT, impaired glucose tolerance; ASO, atherosclerosis obliterans; AP, angina pectoris; MI, myocardial infarction; AMI, acute myocardial infarction.
dysfunction, and valve disease, were less common in those below 10 years old compared with teenagers. These findings are consistent with general aging-associated heart failure, which is attributed to an impairment of the diastolic filling of the left ventricle, rather than a dysfunction of systolic function. A case report of a 14-year-old girl with HGPS described dilated cardiomyopathy with congestive heart failure. Previous reports revealed that progerin is upregulated in human hearts with dilated cardiomyopathy, indicating causal relationships between progerin expression and pathogenesis of cardiomyopathy.

Although it is believed that there is no difference in the disease incidence rate and phenotypes by race, there are relatively few reports from Asia and Africa. Four Japanese and nine Chinese cases were well described by Sato-Kawano et al. and Wang et al., respectively. Also, patients in Africa were reported by two case studies.

**Molecular Mechanism of Progerin Expression**

Lamin is a constituent of the lamina, an intermediate filament responsible for the lining structure of the nuclear envelope. There are three types of lamin, namely, lamin A, lamin B, and lamin C. They are involved in the regulation of DNA transcription, replication, repair, and signal transduction from the cytoskeleton to the nucleus by stabilizing the structure of the nuclear envelope and anchoring chromosomes and transcription factors to the nuclear envelope. Diseases caused by lamin abnormalities include HGPS, muscular dystrophy, neuropathy, and atypical WS, which are collectively called laminopathies.

Lamin A/C is translated via alternative splicing from *LMNA*, which is located on the long arm of chromosome 1 and consists of 12 exons. First, prelamin A is translated from *LMNA*. Prelamin A has a CAAX motif (C, cysteine; A, aliphatic amino acid; X, any amino acid) at the C-terminal, which works as an indicator for farnesyltransferase to farnesylate the cysteine residue. Next, Zmpste24, a metalloprotease, cleaves AAX. Then, the remaining cysteine undergoes methylation by isoprenylcysteine carboxyl methyltransferase, and the C-terminal 15 amino acids are removed by Zmpste24 and other endoproteases to form mature lamin A.

A point mutation (c.1824C>T, G608G, a silent mutation) has been found at codon 608 in the 11th exon of *LMNA* in almost all HGPS patients with classical symptoms. This results in an unusual splicing site and a loss of 50 amino acids, including the Zmpste24 recognition site, which leads to the production of progerin, an aberrant protein that remains farnesylated.

Progerin acts in a dominant-negative manner. Due to the affinity of the farnesylated portion to the membrane, it remains bound to the nuclear membrane even during the M phase of the cell cycle, thus inhibiting normal mitosis. Nuclear accumulation of progerin causes abnormal nuclear morphology, dysregulation of other gene expressions, disruption of DNA repair mechanisms, shortening of telomeres, genomic instability, and abnormal mitochondrial function, leading to premature cellular senescence. It has also been reported that H3K9 methylation is reduced in HGPS cells as in normal aging. Interestingly, it is also known that progerin accumulates in cells of healthy older people, and this discovery has brought further attention to HGPS as a model disease of aging.

**Cardiovascular Phenotypes in HGPS Mouse Models**

HGPS patients develop severe vascular changes, primarily vascular smooth muscle cell depletion, calcification, and fibrosis, in addition to electrical and functional abnormalities in the heart. Several HGPS animal models have been created to recapitulate and analyze these phenotypes.

The most widely used animal model is the *Lmna^(G609G)^* mouse. Similar to HGPS patients, this mouse harbors a silent mutation resulting in abnormal splicing and production of progerin; moreover, it has shortened life span and bone abnormalities. Villa-Bellosta et al. found that the aorta of *Lmna^(G609G)^* mice had excessive calcification and that there was insufficient production and extracellular accumulation of pyrophosphate, a major inhibitor of vascular calcification, in primary vascular smooth muscle cells of the aorta, leading to vascular calcification.

On the other hand, *Lmna^(G609G,G609G)^* mice fed a high-fat diet do not develop atherosclerosis as observed in HGPS patients. To address this issue, Hamczyk et al. generated *ApoE/C5-Lmna^(G609G,G609G)^* mice and fed them with a high-fat diet. They were able to develop atherosclerosis and recapitulate most of the cardiovascular phenotypes observed in HGPS patients.

The *Lmna^(G609G)^* mouse also reproduces the electrical phenotype in the heart. Macias et al. reported that cardiomyocytes from *Lmna^(G609G)^* mice show prolonged action potential duration and refractoriness after repolarization, which may be related to the QT prolongation reported in some HGPS patients.
Treatment of HGPS

Currently, there is no fundamental treatment for HGPS. However, the most encouraging recent topic is the farnesyl transferase inhibitors (FTIs) which inhibit the farnesylation of lamin A. In an observational study with a median treatment duration of 2.2 years, 17 of 63 deaths occurred in the untreated group, compared with 4 of 63 deaths in the lonafarnib-treated group, with a hazard ratio of 0.23. While lonafarnib improves cardiovascular phenotypes, the addition of pravastatin and zolendronic acid has been found to be effective in treating musculoskeletal phenotypes.

CRISPR-based therapies are also in the limelight. Two reports of Lmna-targeted knockouts in Lmna mice have observed prolonged lifespan, suppression of cardiac fibrosis, and improvement of vascular smooth muscle in the tunica media of the aortic arch.

Interestingly, in both cases, the most efficiently genetically modified tissue was the liver, suggesting an association between hepatic dysfunction and the HGPS arteriosclerosis phenotype. In another report, mice carrying a mutation of a human HGPS patient (LMNA) were repaired with a base editor, which substitutes A-T to G-C at c.1824 in Lmna.

Although the most genetically repaired tissue was the liver like the above two reports, vascular smooth muscle restoration and adventitial fibrosis suppression were observed. The base editor has been shown to restore angiogenic potential by reducing progerin expression and increasing intracellular nitric oxide levels in HGPS-induced pluripotent stem (iPS) cell-derived endothelial cells in vitro.

Osoirio et al. has reported that treatment of Lmmd mice with morpholino oligos to suppress aberrant splicing leads to an extended lifespan. Recently, it was reported that suppression of abnormal splicing in transgenic mice carrying the human Lmna mutation could also result in up to 61.6% lifespan extension and inhibition of vascular smooth muscle loss in large vessels.

It is epoch-making in that gene therapy can be performed without editing patients’ DNA, and future clinical application is expected.

Werner Syndrome

WS is an autosomal recessive progeroid syndrome, also known as adult progeria, due to the appearance of various premature aging symptoms in adulthood (Table 1). The causative gene is WRN on the short arm of chromosome 8. About 70% of the cases reported to date are Japanese, and 1 in 150 normal Japanese people has a heterozygous mutation. Patients with WS are generally short in stature but normally develop until puberty, and from around their 20s, they exhibit gray hair, hair loss, bird-like face, hoarseness, and scleroderma-like symptoms in the limbs. Later, they develop cataracts, diabetes, osteoporosis, intractable skin ulcers, arteriosclerotic diseases, and malignant tumors (especially non-epithelial malignancy), and most of them die in their 50s.

Clinical Characteristics of WS

One of the most important clinical features of the disease is intractable skin ulcers that occur mainly on the lower limbs, including the toes, heels, and Achilles tendons. In some cases, these ulcers lead to gangrene or osteomyelitis, leading to amputation of the lower extremities. Unlike foot ulcers of diabetes, WS ulcers are characterized by severe pain and subcutaneous calcification, which significantly reduces the patient’s quality of life.

In addition, WS patients often accumulate visceral fat, resulting in diabetes and dyslipidemia based on insulin resistance. On the other hand, because the limbs wither and atrophy like branches, patients’ body shapes are sometimes called Cushing-like appearance. The symptom of loss of muscle mass is called sarcopenia and has become a major topic in geriatrics. In a study of nine patients with WS, all of them met the diagnostic criteria for sarcopenia.

The key signs to clinically suspect WS are the appearance of gray hair and hair loss (attention must be paid to hair dye and wigs) as well as bilateral cataracts under the age of 30. If multiple corn/callus and calcification of the Achilles tendon are observed, patients’ body shapes are sometimes called Cushing-like appearance. The symptom of loss of muscle mass is called sarcopenia and has become a major topic in geriatrics. The diagnosis is best confirmed by genetic testing, which is a major topic in geriatrics. In a study of nine patients with WS, all of them met the diagnostic criteria for sarcopenia.

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Molecular Mechanism of WS

The WRN protein encoded by the WRN gene is a member of the RecQ helicase family together with RecQ1, BLM, RecQ4, and RecQ5 and has DNA helicase activity (the ability to unwind a DNA duplex into a single strand) as well as DNA exonuclease activity. So far, at least 83 mutations have been reported, and several new mutations have been identified in our laboratory. On the other hand, there is no clear correlation between mutation sites and clinical signs.

WRN has a variety of functions, including DNA enzymes.
replication and repair, telomere maintenance, and epigenetic regulation, such as heterochromatinization. Among them, many reports have confirmed the involvement of WRN in DNA double-strand break (DSB) repair. There are two main pathways in DSB repair, namely, non-homologous end joining (NHEJ) and homologous recombination, and the WRN protein is involved in both\(^{62}\). A recent report demonstrated that WRN proteins promote classical-NHEJ and inhibit alternative-NHEJ, leading to repair error suppression\(^{63}\).

In another study, Zhang et al. reported that the WRN protein is involved in the methylation of H3K9, a marker of heterochromatin\(^{64}\). This loss of methylation is also observed in a general aging process, suggesting that WS mimics the general aging from an epigenetic point of view.

In WS, accumulation of DNA mutations, shortening of telomeres, and abnormalities in histone methylation are assumed to be responsible for various pathological conditions. However, the causal relationship between these abnormalities at the molecular level and the pathological conditions remains to be elucidated, and further research is needed.

**Atherosclerotic Diseases in WS**

Atherosclerotic disease is the second leading cause of death in WS\(^{65}\). According to a 2012 report of Japanese patients, the prevalence of vascular disease in WS was 1.1% for cerebral hemorrhage, 2.7% for cerebral infarction, 10.3% for angina and myocardial infarction, and 17.3% for arteriosclerosis obliterans\(^{66}\). The latest report from the Japanese WS Registry revealed a decrease in the prevalence of 0%, 0%, 2.5%, and 15%, respectively\(^{67}\). In addition to the use of statins\(^{68}\), this reduction may be due to the remarkable development of antidiabetic drugs in recent years\(^{67}\). In fact, in some of the case reports of WS in recent years, no obvious atherosclerotic disease was found\(^{69,72}\) or was only slightly present\(^{61,73,74}\). In the case of a patient who died at 76 years of age, there were almost no findings of atherosclerosis in the cerebral arteries, and only calcification without stenosis was observed in the aorta and coronary arteries\(^{75,76}\). In eight genetically diagnosed Chinese WS patients, the atherosclerotic disease was evident in only one patient\(^{77}\).

Dyslipidemia affects 65% to 85% of WS patients\(^{52,67}\). Of those, the frequency of hypertriglyceridemia is somewhat higher. In fact, patients with hypertriglyceridemia accompanied by 3900 mg/dl of triglycerides had advanced three-vessel disease requiring coronary artery bypass surgery\(^{78}\). In addition to statins to hypercholesterolemia, adequate management of hypertriglyceridemia may also be required.

On the other hand, in some cases, severe aortic stenosis, without the requirement of coronary intervention, has become a problem\(^{79,80}\). In addition, cases of heart failure due to impaired coronary microcirculation with no coronary artery stenosis have been reported\(^{81}\). These suggest that arteriosclerosis in WS needs to be comprehensively evaluated.

A mouse model of WS does not develop arteriosclerosis\(^{82}\). A report of knockdown of the WRN gene using human endothelial cells in vitro demonstrated increased expression of inflammation and adhesion molecules\(^{83}\). On the other hand, a report of differentiation of WRN knockout embryonic stem cells into endothelial cells described no phenotypic changes\(^{84}\). Understanding the molecular mechanisms of atherosclerosis in WS requires further investigation.

**Conclusion**

As aforementioned, HGPS and WS are representative diseases of premature aging, and patients suffer from shortened life expectancy and reduced quality of life. One reason for that is because the full picture of their underlying mechanisms is still unclear. Furthermore, we are globally encountering a super-aging society. The study of progeria is extremely significant as it will contribute to the elucidation of the mechanisms of a general aging. The registration of patients into the HGPS and WS registries both in Japan and overseas is currently ongoing, and we expect that the understanding of the natural history of the disease will elucidate the clinical problems that need to be addressed. In addition, analyses using primary patient samples and patient-derived iPS cells are underway, including in our laboratory, using state-of-the-art technologies, such as the genome, transcriptome, and epigenome analyses\(^{85,86}\). These studies are expected to lead to breakthroughs in the treatment of progeria and the study of general aging.

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Conflicts of Interest
The authors declare there are no conflicts of interest related to this work.

References

1) United Nations Department of Economic and Social Affairs, Population Division: World Population Ageing 2020 Highlights: Living arrangements of older persons. 2020; ST/ESA/SER.A/451
2) North BJ and Sinclair DA: The Intersection Between Aging and Cardiovascular Disease. Circ Res, 2012; 110: 1097-1108
3) Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T and Berger JS: Association Between Advanced Age and Vascular Disease in Different Arterial Territories A Population Database of Over 3.6 Million Subjects. J Am Coll Cardiol, 2013; 61: 1736-1743
4) Hennekam RC: Hutchinson-Gilford progeria syndrome: review of the phenotype. Am J Med Genet A, 2006; 140: 2603-2624
5) Gordon LB, Tuminelli K, Andrés V, Campisi J, Kieran MW, Doucette L and Gordon AS: The progeria research foundation 10 th international scientific workshop; researching possibilities, EXTen ding lives – webinar version scientific summary. Aging, 2021; 13:
6) Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, Brewer CC, Zalewski C, Kim HJ, Solomon B, Brooks BP, Gerber LH, Turner ML, Domingo DL, Hart TC, Graf J, Reynolds JC, Gropman A, Yanovski JA, Gerhard-Herman M, Collins FS, Nabel EG, Cannon RO, 3rd, Gahl WA and Introne WJ: Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med, 2008; 358: 592-604
7) Gordon LB, Shappell H, Massaro J, D'Agostino RB, Brazier J, Campbell SE, Kleinman ME and Kieran MW: Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. Jama-Journal of the American Medical Association, 2018; 319: 1687-1695
8) Coppede F: The epidemiology of premature aging and associated comorbidities. Clin Interv Aging, 2013; 8: 1023-1032
9) Stehbens WE, Wakefield SJ, Gilbert-Barness E, Olson RE and Ackerman J: Histological and ultrastructural features of atherosclerosis in progeria. Cardiovasc Pathol, 1999; 8: 29-39
10) Reichel W and Garcia-Bunuel R: Pathologic findings in progeria: myocardial fibrosis and lipofuscin pigment. Am J Clin Pathol, 1970; 53: 243-253
11) Prakash A, Gordon LB, Kleinman ME, Gurary EB, Massaro J, D'Agostino R, Sr., Kieran MW, Gerhard-Herman M and Smoot L: Cardiac Abnormalities in Patients With Hutchinson-Gilford Progeria Syndrome. Jama Cardiol, 2018; 3: 326-334
12) Lakatta EG and Levy D: Arterial and Cardiac Aging: Major Shareholders in Cardiovascular Disease Enterprises. Circulation, 2003; 107: 346-354
13) Hamczyk MR, del Campo L and Andres V: Aging in the Cardiovascular System: Lessons from Hutchinson-Gilford Progeria Syndrome. Annu Rev Physiol, 2018; 80: 27-48
14) Pachajoa H, Claros-Hulbert A, García-Quintero X, Perean L, Ramirez A and Zea-Vera A: Hutchinson–Gilford Progeria Syndrome: Clinical and Molecular Characterization. Appl Clin Genetics, 2020; Volume 13: 159-164
15) Xu S and Jin ZG: Hutchinson-Gilford Progeria Syndrome: Cardiovascular Pathologies and Potential Therapies. Trends Biochem Sci, 2019; 44: 561-564
16) Messner M, Ghadge SK, Goetsch V, Wimmer A, Dorler J, Polzl G and Zaruba MM: Upregulation of the aging related LMNA splice variant progerin in dilated cardiomyopathy. Plos One, 2018; 13: e0196739
17) Gordon LB, Massaro J, D’Agostino RB, Sr., Campbell SE, Brazier J, Brown WT, Kleinman ME, Kieran MW and Progeria Clinical Trials C: Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. Circulation, 2014; 130: 27-34
18) Sato-Kawano N, Takemoto M, Okabe E, Yokote K, Matsuo M, Kosaki R and Ihara K: The clinical characteristics of Asian patients with classical-type Hutchinson-Gilford progeria syndrome: a case series and a literature review. J Eur Acad Dermatol Venereol, 2021; 35: e387-e391
19) Wang S, Yang Z, Xu Z, Chu Y, Liang Y, Wei L, Zhang B, Xu Z and Ma L: Clinical and genetic features of children with Hutchinson-Gilford progeria syndrome: a case series and a literature review. J Eur Acad Dermatol Venereol, 2021; 35: e387-e391
20) Guedenon KM, Doubaj Y, Akolly DAE, Barry Moussa W, Saka B, Adjenou K, Belo M, Pio M, Mihluedo-Agbolan KA, Vonor K, Amedume KM, Tchaou M, Atakouma YD, Gbadoe AD, Dossou CF, Fiaowo M, Gningningke B, Pitche P, Agbere DA and Gnamey DK: Hutchinson-Gilford Progeria Syndrome: Report of the first Togolese case. Am J Med Genet A, 2020; 182: 1316-1320
21) Mutesa L, Pierquin G, Cwiny-Ay N, Buzizi P and Bours AC, Perry MB, Shaheen M, Kennedy BK and Oshima J: LMNA Mutations in Atypical Werner's Syndrome. J Geriatr Cardiol, 2018; 15: 93-98
22) Polzl G and Zaruba MM: Upregulation of the aging related LMNA splice variant progerin in dilated cardiomyopathy. Plos One, 2018; 13: e0196739
23) Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shaheen M, Connelly KN, Gordon LB, Der CJ, Cox AD and Collins FS: Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A, 2005; 102: 12879-12884
24) Cao K, Capell BC, Erdos MR, Djabali K and Collins FS: A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. Proc Natl Acad Sci U S A, 2007; 104: 4949-4954
25) Scaffidi P and Misteli T: Reversal of the cellular
phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. Nat Med, 2005; 11: 440-445
27) Scaffidi P and Misteli T: Lamin A-dependent nuclear defects in human aging. Science, 2006; 312: 1059-1063
28) Benedicto I, Dorado B and Andres V: Molecular and Cellular Mechanisms Driving Cardiovascular Disease in Hutchinson-Gilford Progeria Syndrome: Lessons Learned from Animal Models. Cells, 2021; 10: 1157
29) Osorio FG, Navarro CL, Cadinanos J, Lopez-Mejia IC, Quiros PM, Bartoli C, Rivera J, Tazi J, Guzman G, Varela I, Deperitis D, de Carlos F, Cobo J, Andres V, De Sandre-Giovannoli A, Freije JM, Levy N and Lopez-Otin C: Splicing-directed therapy in a new mouse model of human accelerated aging. Sci Transl Med, 2011; 3: 106ra107
30) Villa-Bellosta R, Rivera-Torres J, Osorio FG, Acín-Pérez R, Enriquez JA, López-Otin C and André V: Defective Extracellular Pyrophosphate Metabolism Promotes Vascular Calcification in a Mouse Model of Hutchinson-Gilford Progeria Syndrome That Is Ameliorated on Pyrophosphate Treatment. Circulation, 2013; 127: 2442-2451
31) Hamczyk MR and Andres V: Vascular smooth muscle cell loss underpins the accelerated atherosclerosis in Hutchinson-Gilford progeria syndrome. Nucleus, 2019; 10: 28-34
32) Hamczyk MR, Villa-Bellosta R, Gonzalez P, Andres-Manzano MJ, Nogales P, Benton JF, Lopez-Otin C and Andres V: Vascular Smooth Muscle-Specific Progerin Expression Accelerates Atherosclerosis and Death in a Mouse Model of Hutchinson-Gilford Progeria Syndrome. Circulation, 2018; 138: 266-282
33) Macias A, Diaz-Larrosa JJ, Blanco Y, Fanjul V, Gonzalez-Gomez C, Gonzalez P, Andres-Manzano MJ, da Rocha AM, Ponce-Balbuena D, Allan A, Filgueiras-Rama D, Jalife J and Andres V: Paclitaxel mitigates structural alterations and cardiac conduction system defects in a mouse model of Hutchinson-Gilford progeria syndrome. Cardiovasc Res, 2021; cvab055-2021
34) Misteli T: Farnesyltransferase inhibition in HGPS. Cell, 2021; 184: 293
35) Voelker R: First Progeria Drug Is Approved. JAMA, 2021; 325: 20-20
36) Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG and Feng LG: A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. J Clin Invest, 2006; 116: 2115-2121
37) Gordon LB, Kleinman ME, Massaro J, D’Agostino RB, Sr., Shappell H, Gerhard-Herman M, Smoot LB, Gordon CM, Cleveland RH, Nazarian A, Snyder BD, Ulrich NJ, Silvera VM, Liang MG, Quinn N, Miller DT, Huh SY, Dowton AA, Littlefield K, Greer MM and Kieran MW: Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. Circulation, 2016; 134: 114-125
38) Cubria MB, Suarez S, Masoudi A, Oftadeh R, Kamalapathy P, DuBose A, Erdos MR, Cabral WA, Karim L, Collins FS, Snyder BD and Nazarian A: Evaluation of musculoskeletal phenotype of the G608G progeria mouse model with lonafarnib, pravastatin, and zoledronic acid as treatment groups. P Natl Acad Sci USA, 2020; 201906713
39) Beyret E, Liao HK, Yamamoto M, Hernandez-Benitez R, Fu Y, Eriksson G, Reddy P and Izipisu Belmonte JC: Single-dose CRISPR-Cas9 therapy extends lifespan of mice with Hutchinson-Gilford progeria syndrome. Nat Med, 2019; 25: 419-422
40) Santiago-Fernandez O, Osorio FG, Quesada V, Rodriguez F, Basso S, Maeso D, Rolas L, Barkaway A, Nourshargh S, Follgathers AR, Freije JMP and Lopez-Otin C: Development of a CRISPR/Cas9-based therapy for Hutchinson-Gilford progeria syndrome. Nat Med, 2019; 25: 423-426
41) Koblan LW, Erdos MR, Wilson C, Cabral WA, Levy JM, Xiong ZM, Tavarez UL, Davidson LM, Gete YG, Mao X, Newby GA, Doherty SP, Narisu N, Sheng Q, Kriilow C, Lin CY, Gordon LB, Cao K, Collins FS, Brown JD and Liu DR: In vivo base editing rescues Hutchinson-Gilford progeria syndrome in mice. Nature, 2021; 589: 608-614
42) Kim JS and Eriksson M: Base Editing in Progeria. N Engl J Med, 2021; 384: 1364-1366
43) Gete YG, Koblan LW, Mao X, Trappo M, Mahadik B, Fisher JP, Liu DR and Cao K: Mechanisms of angiogenic incompetence in Hutchinson-Gilford progeria via downregulation of endothelial NOS. Aging Cell, 2021; e13388
44) Erdos MR, Cabral WA, Tavarez UL, Cao K, Gvozdenovic-Jeremic J, Narisu N, Zerfas PM, Crumley S, Boku Y, Hanson G, Mourich DV, Kole R, Eckhaus MA, Gordon LB and Collins FS: A targeted antisense therapeutic approach for Hutchinson-Gilford progeria syndrome. Nat Med, 2021; 27: 536-545
45) Putteraju M, Jackson M, Klein S, Shilo A, Bennett CF, Gordon L, Rigo F and Misteli T: Systematic screening identifies therapeutic antisense oligonucleotides for Hutchinson–Gilford progeria syndrome. Nat Med, 2021; 1-10
46) Oshima J, Sidorova JM and Monnat RJ, Jr.: Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. Ageing Res Rev, 2017; 33: 105-114
47) Yokote K, Chanprasert S, Lee L, Eirich K, Takemoto M, Watanabe A, Koizumi N, Lessel D, Mori T, Hisama FM, Ladd PD, Angle B, Baris H, Cefle K, Palanduz S, Ozturk F, Chateau A, Deguchi K, Easwar TK, Federico A, Fox A, Grebe TA, Hay B, Nampoothiri S, Seiter K, Streteen E, Pina-Aguilar RE, Poke G, Poot M, Posmyk R, Martin GM, Kubisch C, Schindler D and Oshima J: WRN Mutation Update: Mutation Spectrum, Patient Registries, and Translational Prospects. Hum Mutat, 2017; 38: 7-15
48) Takemoto M, Mori S, Kuzuya M, Yoshimoto S, Shimamoto A, Igarashi M, Tanaka Y, Miki T and Yokote K: Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr Gerontol Int, 2013; 13: 475-481
49) Honjo S, Yokote K, Fujimoto M, Takemoto M, Kobayashi K, Maezawa Y, Shimoyama T, Sato S, Koshizaka M, Takada A, Isisuna H and Saito Y: Clinical outcome and mechanism of soft tissue calcification in Werner syndrome. Rejuvenation Res, 2008; 11: 809-819
50) Yokote K, Honjo S, Kobayashi K, Fujimoto M,
Kawamura H, Mori S and Saito Y: Metabolic improvement and abdominal fat redistribution in Werner syndrome by pioglitazone. J Am Geriatr Soc, 2004; 52: 1582-1583

51) Yamaga M, Takemoto M, Shoji M, Sakamoto K, Yamamoto M, Ishikawa T, Koshizaka M, Maezawa Y, Kobayashi K and Yokote K: Werner syndrome: a model for sarcopenia due to accelerated aging. Aging-US, 2017; 9: 1738-1744

52) Tsukamoto K, Takemoto M, Kubota Y, Taniguchi T, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Mori S, Kuzuaya M and Yokote K: Management guideline for Werner syndrome 2020 1. Dyslipidemia and fatty liver associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 133-138

53) Kuzuya M, Takemoto M, Kubota Y, Taniguchi T, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Mori S, Tsukamoto K and Yokote K: Management guideline for Werner syndrome 2020. 2. Sarcopenia associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 139-141

54) Takemoto M, Kubota Y, Taniguchi T, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Tsukamoto K, Mori S, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020. 3. Diabetes associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 142-145

55) Taniguchi A, Tanaka Y, Takemoto M, Kubota Y, Taniguchi T, Motegi SI, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Tsukamoto K, Mori S, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020 8. Calcification in tendons associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 163-165

56) Motegi SI, Takemoto M, Taniguchi T, Kubota Y, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Mori S, Tsukamoto K, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020. 7. Skin ulcer associated with Werner syndrome: Dermatological treatment. Geriatr Gerontol Int, 2021; 21: 160-162

57) Kubota Y, Takemoto M, Taniguchi T, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Mori S, Tsukamoto K, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020 6. Skin ulcers associated with Werner syndrome: Prevention and non-surgical and surgical treatment. Geriatr Gerontol Int, 2021; 21: 153-159

58) Taniguchi T, Takemoto M, Kubota Y, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Mori S, Tsukamoto K, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020. 5. Infection associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 150-152

59) Mori S, Takemoto M, Kubota Y, Taniguchi T, Motegi SI, Taniguchi A, Nakagami H, Maezawa Y, Koshizaka M, Kato H, Tsukamoto K, Kuzuya M and Yokote K: Management guideline for Werner syndrome 2020. 4. Osteoporosis associated with Werner syndrome. Geriatr Gerontol Int, 2021; 21: 146-149

60) Croteau DL, Popuri V, Opresko PL and Bohr VA: Human RecQ helicases in DNA repair, recombination, and replication. Annu Rev Biochem, 2014; 83: 519-552

61) Maezawa Y, Kato H, Takemoto M, Watanabe A, Koshizaka M, Ishikawa T, Sorgolzaeaval F, Kuzuya M, Wakabayashi H, Kusaka T, Yokote K and Oshima J: Biallelic WRN Mutations in Newly Identified Japanese Werner Syndrome Patients. Mol Syndromol, 2018; 9: 214-218

62) Rossi ML, Ghosh AK and Bohr VA: Roles of Werner syndrome protein in protection of genome integrity. DNA Repair (Amst), 2010; 9: 331-344

63) Shamanna RA, Lu HM, de Freitas JK, Tian J, Croteau DL and Bohr VA: WRN regulates pathway choice between classical and alternative non-homologous end joining. Nat Commun, 2016; 7: 13785

64) Zhang W, Li J, Suzuki K, Qu J, Wang P, Zhou J, Liu X, Ren R, Xu X, Ocampo A, Yuan T, Yang J, Li Y, Shi L, Guan D, Pan H, Duan S, Ding Z, Li M, Yi F, Bai R, Wang Y, Chen C, Yang F, Li X, Wang Z, Aizawa E, Goebel A, Soligalla RD, Reddy P, Esteban CR, Tang F, Liu GH and Belmonte JC: Aging stem cells. A Werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. Science, 2015; 348: 1160-1163

65) Goto M, Ishikawa Y, Sugimoto M and Furuchi Y: Werner syndrome: a changing pattern of clinical manifestations in Japan (1917-2008). Biosci Trends, 2013; 7: 13-22

66) Okabe E, Takemoto M, Onishi S, Ishikawa T, Ishibashi R, He P, Kobayashi K, Fujimoto M, Kawamura H and Yokote K: Incidence and characteristics of metabolic disorders and vascular complications in individuals with Werner syndrome in Japan. J Am Geriatr Soc, 2012; 60: 997-998

67) Koshizaka M, Maezawa Y, Maeda Y, Shoji M, Kato H, Kaneko H, Ishikawa T, Kinoshita D, Kobayashi K, Kawashima J, Sekiguchi A, Motegi S, Nakagami H, Yamada Y, Tsukamoto S, Taniguchi A, Sugimoto K, Shoda Y, Hashimoto K, Yoshimura T, Suzuki D, Kuzuya M, Takemoto M and Yokote K: Time gap between the onset and diagnosis in Werner syndrome: a nationwide survey and the 2020 registry in Japan. Aging-US, 2020; 12: 24940-24956

68) Yokote K and Saito Y: Extension of the life span in patients with Werner syndrome. J Am Geriatr Soc, 2008; 56: 1770-1771

69) Yamamoto R, Akasaki K, Horita M, Yonezawa M, Asakura H, Kanamori T, Maezawa Y, Koshizaka M, Yokote K and Kurita S: Evaluation of glucose tolerance and effect of dietary management on increased visceral fat in a patient with Werner syndrome. Endocr J, 2020; 67: 1239-1246

70) Rincon A, Mora L, Suarez-Olband F and Rojas JA: Werner's Syndrome: Understanding the Phenotype of Premature Aging-First Case Described in Colombia. Case Rep Genet, 2019; 2019: 8538325

71) Matsumoto N, Ohta Y, Deguchi K, Kishida M, Sato K, Shang J, Takemoto M, Hishikawa N, Yamashita T, Watanabe A, Yokote K, Takemoto M, Oshima J and Abe K: Characteristic Clinical Features of Werner Syndrome with a Novel Compound Heterozygous WRN Mutation c.1720+1G>A Plus c.3139-1G>C. Intern Med, 2019; 58: 1033-1036
72) Ingegnoli F and Crotti C: Nailfold scleroderma-like capillary abnormalities in Werner syndrome (adult progeria). Vasc Med, 2017; 22: 246-247
73) Singh A, Ganguly S, Chhabra N, Yadav H and Oshima J: A Case Report of Werner’s Syndrome With a Novel Mutation From India. Cureus, 2020; 12: e8025
74) He J, Pan D, Wu P and Tang J: Recurrent skin ulcer cross-repair and sensory reconstruction in a WRN gene mutational patient. An Bras Dermatol, 2018; 93: 443-446
75) Kuzuya M, Shi RQ, Yanagawa M, Watanabe K, Samizo S and Ando R: Long-lived Werner syndrome patient autopsy report: The presence of liver cirrhosis. Geriatr Gerontol Int, 2021; 21: 433-435
76) Kuzuya M, Shi RQ, Yanagawa M, Watanabe K, Samizo S, Ando R, Miyahara H, Iwasaki Y and Yoshida M: Cerebral pathological findings in long-lived patient with Werner syndrome and dementia. Geriatr Gerontol Int, 2021;
77) Li H, Yang M, Shen H, Wang S and Cai H: Severe metabolic disorders coexisting with Werner syndrome: a case report. Endocr J, 2021; 68: 261-267
78) Kaur A, Grover P, Albawaliz A, Chauhan M and Barthel B: Growing Old Too Fast: A Rare Case of Werner Syndrome. Cureus, 2019; 11: e4743
79) Handa K, Fukui S, Shirakawa Y, Sakamoto T, Kitahara M, Kakizawa Y and Nishi H: Aortic valve replacement with annular patch enlargement for a patient with Werner’s syndrome and severe aortic stenosis. J Cardiothorac Surg, 2020; 15: 174
80) Masada K, Kuratani T, Maeda K, Torikai K and Sawa Y: Transcatheter aortic valve replacement in a patient with Werner syndrome. J Card Surg, 2017; 32: 414-415
81) Yamamoto M, Yamamoto E, Yasuda O, Yasuda H, Sakamoto K, Tsujita K, Izumiya Y, Kaikita K, Hokimoto S and Ogawa H: A case of Werner’s syndrome with cardiac syndrome X and heart failure with preserved ejection fraction. J Cardiol Cases, 2015; 12: 195-198
82) Chang S, Multani AS, Cabrera NG, Naylor ML, Laud P, Lombard D, Pathak S, Guarente L and DePinho RA: Essential role of limiting telomeres in the pathogenesis of Werner syndrome. Nat Genet, 2004; 36: 877-882
83) Laarmann K, Kress JM, Kaina B and Fritz G: Werner syndrome (WRN) DNA helicase and base excision repair (BER) factors maintain endothelial homeostasis. DNA Repair (Amst), 2019; 73: 17-27
84) Wu Z, Zhang W, Song M, Wang W, Wei G, Li W, Lei J, Huang Y, Sang Y, Chan P, Chen C, Qu J, Suzuki K, Belmonte JCI and Liu GH: Differential stem cell aging kinetics in Hutchinson-Gilford progeria syndrome and Werner syndrome. Protein Cell, 2018; 9: 333-350
85) Kato H, Maezawa Y, Ouchi Y, Takayama N, Sone M, Sone K, Takada-Watanabe A, Tsujimura K, Koshizaka M, Nagasawa S, Saitoh H, Ohtaka M, Nakanishi M, Tahara H, Shimamoto A, Iwama A, Eto K and Yokote K: Generation of disease-specific and CRISPR/Cas9-mediated gene-corrected iPS cells from a patient with adult progeria Werner syndrome. Stem Cell Res, 2021; 53: 102360
86) Kato H, Maezawa Y, Takayama N, Ouchi Y, Kaneko H, Kinoshita D, Takada-Watanabe A, Oshima M, Koshizaka M, Ogata H, Kubota Y, Mitsukawa N, Iwama A and Yokote K: Fibroblasts from different body parts exhibit distinct phenotypes in adult progeria Werner syndrome. Aging (Albany NY), 2021; 13: 4946-4961
87) Satoh M, Imai M, Sugimoto M, Goto M and Furuichi Y: Prevalence of Werner’s syndrome heterozygotes in Japan. Lancet, 1999; 353: 1766
88) Huang S, Lee L, Hanson NB, Lenaerts C, Hoehn H, Poot M, Rubin CD, Chen DF, Yang CC, Juch H, Dorn T, Spiegel R, Oral EA, Abid M, Battisti C, Lucci-Cordisco E, Neri G, Steed EH, Kidd A, Isley W, Showalter D, Vitone JL, Konstantinow A, Ring J, Meyer P, Wengeler SL, von Herbay A, Wollina U, Schuelke M, Huizenga CR, Leistritz DF, Martin GM, Mian IS and Oshima J: The spectrum of WRN mutations in Werner syndrome patients. Hum Mutat, 2006; 27: 558-567