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Progeria Syndrome: Unravelling the Mystery of Premature Aging in Children

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Abstract

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic condition marked by rapid aging in children, primarily resulting from mutations in the LMNA gene. This review article delves into the clinical manifestations, underlying mechanisms, and prevalence of HGPS, emphasizing common symptoms such as growth delays, hair loss, and cardiovascular issues that often lead to premature death. It further investigates the molecular processes associated with the disorder, focusing on progerin production—an abnormal protein that interferes with cellular operations and accelerates aging. The article also reviews current diagnostic methods, including genetic analyses and imaging findings, alongside ongoing clinical trials exploring potential treatments like Lonafarnib. While there have been notable advancements in research and therapeutic approaches, challenges persist in finding reliable biomarkers and comprehending the full effects of HGPS on those affected. This review seeks to offer a thorough understanding of progeria, highlighting the necessity for ongoing research to enhance diagnostic and treatment options for this challenging condition.

Keywords: Progeria

Introduction

Hutchinson-Gilford progeria syndrome (HGPS), commonly referred to as progeria, is an extremely rare genetic disorder characterized by accelerated aging in children. This condition affects approximately 1 in every 4 to 8 million live births (1-3). Infants with HGPS typically appear healthy at birth but begin to show signs of aging within their first year, including growth delays, alopecia (hair loss), and skin changes resembling scleroderma (4-7). Other symptoms include a lack of subcutaneous fat, skeletal abnormalities, and joint stiffness. The average life expectancy

for individuals with this syndrome is around 13 years, with most succumbing to cardiovascular diseases and related complications (8,9). The primary cause of HGPS is a de novo mutation in the LMNA gene, specifically a single nucleotide changes in exon 11 (c.1824C>T, p.G608G), which accounts for about 90% of cases. This gene encodes lamin A, a crucial protein that provides structural support to the nuclear envelope. The mutation leads to the production of an abnormal protein known as progerin, which disrupts normal cellular functions by altering the processing of prelamin A (10). As a result, progerin remains improperly modified and associates abnormally with the nuclear membrane, leading to significant cellular dysfunction (11). The cellular manifestations of HGPS include distinctive features observed in fibroblasts from affected individuals, such as nuclear blebbing, thickened nuclear laminae, and abnormal distributions of nuclear pore complexes. These alterations contribute to a loss of peripheral heterochromatin and have been linked to changes in gene expression profiles within these cells. Interestingly, progerin has also been detected in normal cells, suggesting that the underlying mechanisms of progeria may share similarities with those involved in typical aging processes (12-14). A proposed mechanism for HGPS suggests that the disease leads to premature depletion of stem cells, impairing tissue regeneration capacity. This theory posits that tissues subjected to continuous mechanical stress or those requiring high cell turnover—such as skin—experience accelerated exhaustion of their progenitor cells (15,16). Supporting evidence comes from studies indicating that expression of progerin triggers differentiation in human mesenchymal stem cells (17). Furthermore, research involving induced pluripotent stem cells (iPSCs) derived from HGPS patients has indicated a potential link between stem cell depletion and increased sensitivity to hypoxic conditions. To investigate this hypothesis further, researchers have utilized mouse models that replicate several characteristics of the HGPS skin phenotype (18,19). Previous findings from these models demonstrated that postnatal expression of the HGPS mutation results in a progressive phenotype marked by initial epidermal hyperplasia followed by advanced stages characterized by epidermal hypoplasia and fibrotic changes in the dermis (20). While other models of accelerated aging have shown reduced stem cell populations and impaired function, there remains a lack of evidence directly linking human premature aging syndromes like HGPS to stem cell depletion (21).

Epidemiology and prevalence of Progeria Syndrome

The prevalence of Hutchinson-Gilford progeria syndrome (HGPS) is estimated to be between 1 in 4 to 8 million live births, making it an extremely rare condition (22). This syndrome does not show any significant differences based on gender, ethnicity, or geographic location, and it is generally regarded as sporadic in nature. Currently, approximately 114 children diagnosed with HGPS are reported across 39 countries. The average lifespan for these individuals is around 13.5 years, with a life expectancy range of 8 to 21 years (23). Most deaths result from cardiovascular issues such as strokes, heart attacks, or heart failure. HGPS is classified as an ultra-rare autosomal dominant orphan disease that affects both sexes equally and does not favor any ethnic group. The condition typically manifests in early childhood and has an overall prevalence estimated at 1 in 18 million. In 2014, it was estimated that around 300 to 350 children were living with progeria globally. According to the Progeria Research Foundation's International Registry, by September 2015, there were 125 children identified across 43 countries (24). The incidence rate is noted as approximately one in every 4 million births, with an average life expectancy of about 14.6 years, ranging from as low as 1.6 years to as high as 27.5 years. Notably, while children with various progeroid

syndromes experience numerous physical symptoms such as growth delays and skin changes, their cognitive functions typically remain intact (25,26).

Etiology and common symptoms of Progeria syndrome

Classical Hutchinson-Gilford progeria syndrome (HGPS) is primarily caused by a sporadic autosomal dominant mutation, although there are rare inheritable forms like Werner's syndrome (27). There exist atypical variants known as non-classical progeria, which present with milder growth retardation, slower hair loss, delayed onset of lipodystrophy, and more pronounced osteolysis, particularly in areas other than the face. Individuals with non-classical HGPS often survive into adulthood and inherit the condition in an autosomal recessive manner. Typically HGPS arises from a de novo point mutation in the DNA (28). Affected children appear normal at birth but experience significant weight loss and growth failure within their first year. By 18 to 24 months, they exhibit signs such as a thin physique, a small facial structure relative to their head size, high-pitched voices, irregular teeth alignment, a pinched nose, and notably large, prominent eyes. Other physical characteristics include underdeveloped clavicles and lack of sexual maturation. Over time, these children lose body fat and eyelashes, leading to complete baldness (alopecia). Their skin becomes fragile and translucent, revealing underlying veins. Common health issues include angina, hypertension, joint stiffness, and hip dislocations (29). Clinical evaluations reveal prolonged prothrombin times and elevated platelet counts, which are not typical of normal aging processes. Biochemical tests generally yield normal results except for increased levels of low-density lipoproteins and cholesterol in the blood, along with heightened urinary excretion of hyaluronic acid (HA) (30). It is estimated that these children biologically age around ten years for every calendar year. Remarkably they maintain normal cognitive abilities and intelligence levels. However, there has been limited research into the signalling pathways or neurochemical profiles in the brains of these individuals (31). Therefore, it remains plausible that brain signalling mechanisms are involved in the disease's development. Heart disease progresses rapidly in these children by approximately age 13, mirroring the prevalence seen in the general population around their sixties. Notably, there has been only one documented case of a patient living up to 45 years (32).

Pathophysiology of Progeria syndrome

Mutations in the LMNA gene, which encodes the proteins lamin A and C, lead to significant disruptions in various cellular processes, including DNA replication and repair, gene transcription and silencing, nuclear pore complex positioning, chromatin remodeling, and the dynamics of the nuclear envelope during cell division (33-36). Over 400 mutations in this gene have been linked to a wide range of degenerative diseases, including neuropathies, muscular dystrophies, lipodystrophies, and disorders associated with premature aging. Among the most severe conditions arising from these mutations are Hutchinson-Gilford Progeria Syndrome (HGPS) and Restrictive Dermopathy (37-39). HGPS is a rare but severe condition where affected individuals appear healthy at birth but develop pronounced growth abnormalities within their first two years (40). These children exhibit features associated with accelerated aging and typically succumb to cardiovascular issues related to atherosclerosis by their teenage years. In contrast, Restrictive Dermopathy presents with even more severe symptoms, including significant growth retardation and limited movement while in utero, often resulting in death shortly after birth (40,41). Both HGPS and Restrictive Dermopathy stem from mutations that interfere with the normal conversion of prelamin A

into lamin A. This conversion process involves several steps, beginning with farnesylation at the C-terminal 'CaaX' motif of prelamin A (42). Following this, endopeptidases such as Rce1 or Zmpste24 cleave the -aaX sequence, after which the terminal cysteine undergoes carboxymethylation by Icmt (isoprenyl cysteine carboxyl methyltransferase). A subsequent cleavage by Zmpste24 removes an additional 15 amino acids, including the farnesylated cysteine, resulting in mature lamin A (43-46). The majority of HGPS cases involve a specific de novo heterozygous silent mutation (c.1827C > T, G608G) located in exon 11 of the LMNA gene. This mutation activates a cryptic splice site in mRNA, leading to a deletion of 50 amino acids that includes the critical Zmpste24 cleavage site near the C-terminus of prelamin A (47). The outcome is the production of progerin, a permanently farnesylated and carboxymethylated protein that disrupts nuclear architecture, alters heterochromatin positioning within the nucleus, modifies epigenetic regulation, affects signalling pathways and gene expression, destabilizes telomeres, induces genomic instability, and accelerates cellular senescence (48). Restrictive Dermopathy results from prelamin A accumulation due to missense mutations in LMNA or due to loss-of-function mutations affecting Zmpste24. These genetic alterations highlight the critical role of proper lamin processing in maintaining cellular function and integrity (49).

Experimental models of progeria

To enhance the understanding of the pathogenesis and progression of progeroid syndromes (PSs) and to explore potential therapeutic avenues, researchers worldwide have focused on developing various animal models (50). For instance, Lmna−/− mice exhibit cardiac and skeletal muscle abnormalities akin to those seen in Emery-Dreifuss muscular dystrophy in humans. Another study found that homozygous mice with an autosomal recessive mutation in the Lmna gene display characteristics similar to HGPS, including significant growth delays, skin and bone pathologies, and typically die within 4 to 5 weeks (51,52). Additionally, Ercc1−/− mice, which are deficient in DNA repair, show slight delays in embryonic and early postnatal development; however, their growth nearly halts by the second week after birth, leading to death by four weeks (53). These mice also present with various issues such as skin, liver, and bone marrow pathologies, progressive ataxia, and signs of premature aging. Zmpste24−/− mice appear normal at birth but soon develop progeroid symptoms like hair loss, spinal deformities, and dental and bone abnormalities (54). Treatment with a protein farnesyltransferase inhibitor (FTI) can alleviate some of these symptoms. These Zmpste24−/− mice also show elevated levels of growth hormone (GH) along with significantly reduced plasma insulin-like growth factor 1 (IGF-1), both of which are crucial for regulating longevity. Administering recombinant IGF-1 helps restore the balance between GH and IGF-1 in these mice, delaying the onset of many progeroid features and significantly extending their lifespan (55). In vitro studies have suggested that FTIs may play a role in treating HGPS as well. A recent investigation demonstrated that rapamycin can inhibit abnormal mTORC1 signalling in Lmna−/− mice, leading to improved cardiac and skeletal muscle functions and enhancing their survival rates. These findings underscore the potential for targeted therapies to mitigate the effects of progeroid syndromes through various molecular pathways (56).

Current status of diagnosis, drugs and medication

Despite ongoing efforts to find an effective treatment for Hutchinson-Gilford Progeria Syndrome (HGPS), there is currently no diagnostic kit available for its early detection. Typically, diagnosis begins with a clinical evaluation

based on observable phenotypic traits and the child's medical history. Following this assessment, genetic testing for mutations in the LMNA gene is commonly performed to confirm the diagnosis of HGPS and to facilitate early intervention in treatment (57). A case report has indicated that clinical diagnosis can also be supported by specific radiological findings, such as diastasis of the sagittal suture accompanied by multiple Wormian bones in the skull, a hypoplastic mandible with an infantile angle, fish mouth vertebrae, bilateral coxa valga deformity, and resorption of terminal phalanges. In collaboration with organizations like the Progeria Research Foundation, the National Institutes of Health, Boston Children's Hospital, and Dana-Farber Cancer Institute, a clinical drug trial was launched in 2010 to evaluate the effectiveness of three promising drugs: Pravastatin (a statin used to lower cholesterol and prevent heart disease), Zoledronic acid (a bisphosphonate for treating osteoporosis and preventing fractures), and Lonafarnib (a farnesyltransferase inhibitor that has shown potential in reversing progeroid features in various mouse models). This trial involved 25 children with progeria over a two-year period and reported that Lonafarnib successfully promoted weight gain while improving cardiovascular and skeletal issues (58). This represents a significant advancement in progeria research and may lead to the development of definitive treatments for this rare and complex syndrome.

Scope for future research

Progeria, or Hutchinson-Gilford Progeria Syndrome (HGPS), is a rare condition that poses challenges for research due to its infrequency (59,60). However, the efforts of affected children's families, along with various research groups and the Progeria Research Foundation (PRF), have significantly raised awareness about the syndrome. Research has suggested potential biomarkers for HGPS, such as elevated levels of hyaluronic acid (HA). Yet, some studies have contradicted this notion, indicating that HA levels in the urine and serum of HGPS patients are similar to those of healthy controls (61). A comprehensive analysis by Gordon and colleagues examined serum and urinary hyaluronidases using both quantitative (ELISA) and qualitative (gel detection) methods, ultimately disputing the validity of HA as a reliable marker for HGPS. Consequently, the search continues for a definitive and accessible diagnostic marker (62). Proteins associated with HGPS are thought to play a crucial role in the aging process, which may contribute to the increased risk of premature heart disease in these children. Investigations into factors like IGF-1 signalling and hormonal cascades in existing aging models have revealed significant deviations from normal parameters. These deviations could stem from issues related to the pituitary gland or other organs, defects in micronutrient metabolism (such as vitamin D), abnormal protein glycation, imbalances in antioxidant levels, or other physiological processes (63). Research has shown that WNIN/Ob rats, which are obese models developed by the Wistar Institute of Nutrition, exhibit signs of premature aging, including tumor development and immune response deficiencies. It is essential to analyse these animal models for their genomic, proteomic, and biochemical profiles to identify shared or potentially faulty pathways that may contribute to the understanding of progeria and related disorders (64).

Conclusion

The field of gerontology has gained recognition relatively recently compared to other research disciplines. Currently, researchers are dedicating significant efforts to delay the natural aging process and mitigate the associated physical, psychological, and social challenges. While the inheritance pattern of Hutchinson-Gilford Progeria

Syndrome (HGPS) is established, it primarily presents as a sporadic condition. Therefore, investigating the underlying cellular and molecular mechanisms that contribute to accelerated aging and the rapid progression of HGPS is essential for effective intervention.

Reference

1. DeBusk FL (1972) The Hutchinson-Gilford progeria syndrome. Report of 4 cases and review of the literature. J. Pediatr. 80, 697–724.

2. Brown WT (1992) Progeria: a human-disease model of accelerated aging. Am. J. Clin. Nutr. 55, 1222S–1224S.

3. 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 III RO, Gahl WA, Introne WJ (2008) Phenotype and course of Hutchinson-Gilford progeria syndrome. N. Engl. J. Med. 358, 592–604.

4. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Le´ vy N (2003) Lamin A truncation in Hutchinso.

5. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 423, 293–298.

6. Dechat T, Pfleghaar K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD (2008) Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. Genes Dev. 22, 832–853.

7. Capell BC, Collins FS (2006) Human laminopathies: nuclei gone genetically awry. Nat. Rev. Genet. 7, 940–952.

8. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS (2004) Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. Proc. Natl Acad. Sci. USA 101, 8963–8968.

9. Csoka AB, English SB, Simkevich CP, Ginzinger DG, Butte AJ, Schatten GP, Rothman FG, Sedivy JM (2004) Genome-scale expression profiling of Hutchinson Gilford progeria syndrome reveals widespread transcriptional misregulation leading to mesodermal / mesenchymal defects and accelerated atherosclerosis. Aging Cell 3, 235–243.

10. Ly DH, Lockhart DJ, Lerner RA, Schultz PG (2000) Mitotic misregulation and human aging. Science 287, 2486–2492.

11. Scaffidi P, Misteli T (2006) Lamin A-dependent nuclear defects in human aging. Science 312, 1059–1063.

12. Rodriguez S, Coppede` F, Sagelius H, Eriksson M (2009) Increased expression of the Hutchinson-Gilford progeria syndrome truncated lamin A transcript during cell aging. Eur. J. Hum. Genet. 7, 928–937.

13. McClintock D, Ratner D, Lokuge M, Owens DM, Gordon LB, Collins FS, Djabali K (2007) The mutant form of lamin A that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. PLoS ONE 12, e1269.

14. Halaschek-Wiener J, Brooks-Wilson A (2007) Progeria of stem cells: stem cell exhaustion in Hutchinson-Gilford progeria syndrome. J. Gerontol. A Bio. Sci. Med. Sci. 62, 3–8.

15. Scaffidi P, Misteli T (2008) Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. Nat. Cell Biol. 10, 452–459.

16. Zhang J, Lian Q, Zhu G, Zhou F, Sui L, Tan C, Mutalif RA, Navasankari R, Zhang Y, Tse HF, Stewart CL, Colman A (2011) A human iPSC model of Hutchinson Gilford Progeria reveals vascular smooth muscle and mesenchymal stem cell defects. Cell Stem Cell 1, 31–45.

17. Sagelius H, Rosengardten Y, Hanif M, Erdos MR, Rozell B, Collins FS, Eriksson M (2008a) Targeted transgenic expression of the mutation causing Hutchinson Gilford progeria syndrome leads to proliferative and degenerative epidermal disease. J. Cell Sci. 121, 969–978.

18. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI (1997) Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 390, 45–51.

19. Waikel RL, Kawachi Y, Waikel PA, Wang XJ, Roop DR (2001) Deregulated expression of c-Myc depletes epidermal stem cells. Nat. Genet. 28, 165–168.

20. Liu H, Fergusson MM, Castilho RM, Liu J, Cao L, Chen J, Malide D, Rovira II, Schimel D, Kuo CJ (2007) Augmented Wnt signaling in a mammalian model of accelerated aging. Science 317, 803–806.

21. Su X, Paris M, Gi YJ, Tsai KY, Cho MS, Lin YL, Biernaskie JA, Sinha S, Prives C, Pevny LH, Miller FD, Flores ER (2009) TAp63 prevents premature aging by promoting adult stem cell maintenance. Cell Stem Cell 5, 64–75.

22. Progeria Research Foundation (PRF) webpage. Available from: http://www.progeriaresearch.org/meet_the_kids.html, accessed on May 17, 2014.

23. Sandre-Giovannoli A, et al. HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. Mech Ageing Dev 2008; 129 : 449-59.

24. Hennekam RC. Hutchinson-Gilford progeria syndrome: review of the phenotype. Am J Med Genet A 2006; 140 : 2603-24.

25. Shalev SA, De Sandre-Giovannoli A, Shani AA, Levy N. An association of Hutchinson-Gilford progeria and malignancy. Am J Med Genet A 2007; 143: 1821-6.

26. Gordon LB, Mccarten KM, Giobbie-Hurder A et al. (2007). Disease progression in Hutchinson–Gilford progeria syn drome: impact on growth and development. Pediatrics 120: 824–833.

27. Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, et al. Positional cloning of the Werner's syndrome gene. Science 1996; 272 : 258-62.

28. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 2003; 423 : 293-8.

29. Espandar R, Eraghi AS, Mardookhpour S. Simultaneous shoulder and hip dislocation in a 12-year-old girl with Hutchinson-Gilford progeria syndrome. Acta Med Iran 2012; 50 : 439-43.

30. Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, et al. Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med 2008; 358 : 592-604.

31. Rastogi R, Chander Mohan SM. Progeria syndrome: a case report. Indian J Orthop 2008; 42 : 97-9.

32. Young SG, Fong LG, Michaelis S. Prelamin A, Zmpste24, misshapen cell nuclei, and progeria--new evidence suggesting that protein farnesylation could be important for disease pathogenesis. J Lipid Res 2005; 46 : 2531-58.

33. Goldman RD, Gruenbaum Y, Moir RD, Shumaker DK, Spann TP: Nuclear lamins: building blocks of nuclear architecture. Genes Dev 2002, 16:533-547.

34. Gruenbaum Y, Margalit A, Goldman RD, Shumaker DK, Wilson KL: The nuclear lamina comes of age. Nat Rev Mol Cell Biol 2005, 6:21-31.

35. Worman HJ: Nuclear lamins and laminopathies. J Pathol 2012, 226:316-325.

36. Mekhail K, Moazed D: The nuclear envelope in genome organization, expression and stability. Nat Rev Mol Cell Biol 2010, 11:317-328.

37. Broers JL, Ramaekers FC, Bonne G, Yaou RB, Hutchison CJ: Nuclear lamins: laminopathies and their role in premature ageing. Physiol Rev 2006, 86:967-1008.

38. Bertrand AT, Chikhaoui K, Yaou RB, Bonne G: Clinical and genetic heterogeneity in laminopathies. Biochem Soc Trans 2011, 39:1687-1692.

39. Navarro CL, De Sandre-Giovannoli A, Bernard R, Boccaccio I, Boyer A, Genevieve D, Hadj-Rabia S, Gaudy-Marqueste C, Smitt HS, Vabres P et al.: Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. Hum Mol Genet 2004, 13:2493-2503.

40. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, Erdos MR, Blair C, Funke B, Smoot L et al.: Cardiovascular pathology in Hutchinson–Gilford progeria: correlation with the vascular pathology of aging. Arterioscler Thromb Vasc Biol 2010, 30: 2301-2309.

41. Pereira S, Bourgeois P, Navarro C, Esteves-Vieira V, Cau P, De Sandre-Giovannoli A, Levy N: HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. Mech Ageing Dev 2008, 129:449-459.

42. Hennekam RC: Hutchinson–Gilford progeria syndrome: review of the phenotype. Am J Med Genet A 2006, 140:2603-2624.

43. Rusinol AE, Sinensky MS: Farnesylated lamins, progeroid syndromes and farnesyl transferase inhibitors. J Cell Sci 2006, 119:3265-3272.

44. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M et al.: Lamin a truncation in Hutchinson–Gilford progeria. Science 2003, 300:2055.

45. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P et al.: Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. Nature 2003, 423:293-298.

46. Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen DJ et al.: Genomic instability in laminopathy-based premature aging. Nat Med 2005, 11: 780-785.

47. Viteri G, Chung YW, Stadtman ER: Effect of progerin on the accumulation of oxidized proteins in fibroblasts from Hutchinson Gilford progeria patients. Mech Ageing Dev 2010, 131:2-8.

48. Scaffidi P, Misteli T: Lamin A-dependent nuclear defects in human aging. Science 2006, 312:1059-1063.

49. Burtner CR, Kennedy BK: Progeria syndromes and ageing: what is the connection? Nat Rev Mol Cell Biol 2010, 11:567-578.

50. Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Naqashima K, et al. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. J Cell Biol 1999; 147 : 913-20.

51. Mounkes LC, Kozlov S, Hernandez L, Sullivan T, Stewart CL. A progeroid syndrome in mice is caused by defects in A-type lamins. Nature 2003; 423 : 298-301.

52. Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, et al. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. Nature 2006; 444 : 1038-43.

53. Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, et al. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. Proc Natl Acad Sci USA 2002; 99 : 13049-54.

54. Pendás AM, Zhou Z, Cadiñanos J, Freije JM, Wang J, Hultenby K, et al. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. Nat Genet 2002; 31 : 94-9.

55. Russell SJ, Kahn CR. Endocrine regulation of ageing. Mol Cell Biol 2007; 8 : 681-91.

56. Ramos FJ, Chen SC, Garelick MG, Dai DF, Liao CY, Schreiber KH, et al. Rapamycin reverses elevated mTORC1 signalling in lamin A/C-deficient mice, rescues cardiac and skeletal muscle function, and extends survival. Sci Transl Med 2012; 4 : 144ra103.

57. Rastogi R, Chander Mohan SM. Progeria syndrome: a case report. Indian J Orthop 2008; 42 : 97-9.

58. Gordon LB, Massaro J, D'Agostino RB Sr, Campbell SE, Brazier J, Brown WT, et al. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. Circulation. In press: 2014.

59. Kieras FJ, Brown WT, Houck GE, Jr., Zebrower M. Elevation of urinary hyaluronic acid in Werner's syndrome and progeria. Biochem Med Metab Biol 1986; 36 : 276-82.

60. Zebrower M, Kieras FJ, Brown WT. Urinary hyaluronic acid elevation in Hutchinson-Gilford progeria syndrome. Mech Ageing Dev 1986; 35 : 39-46.

61. Gordon LB, Harten IA, Calabro A, Sugumaran G, Csoka AB, Brown WT, et al. Hyaluronan is not elevated in urine or serum in Hutchinson-Gilford progeria syndrome. Hum Genet 2003; 113 : 178-87.

62. Bandaru P, Rajkumar H, Nappanveettil G. Altered or impaired immune response upon vaccination in WNIN/Ob rats. Vaccine 2011; 29 : 3038-42.

63. Harishankar N, Vajreswari A, Giridharan NV. WNIN/GR-Ob - an insulin-resistant obese rat model from inbred WNIN strain. Indian J Med Res 2011; 134 : 320-9.

64. Sinha JK, Ghosh S, Swain U, Giridharan NV, Raghunath M. Increased macromolecular damage due to oxidative stress in the neocortex and hippocampus of WNIN/Ob, a novel rat model of premature aging. Neuroscience 2014; 269 : 256-64.