Progeria: A Rare Genetic Syndrome

Veena Sharma¹ · Richa Shukla¹

Received: 14 July 2019 / Accepted: 9 September 2019 / Published online: 25 September 2019
© Association of Clinical Biochemists of India 2019

Abstract An uncommon deadly genetic situation symbolized by the presence of rapid maturation in infants is called as the Hutchinson–Gilford Progeria Syndrome. The term basically is meant as ‘prematurely old’ taken from the Greek meanings. The selective cause behind this syndrome is usually a mutation in a gene called LMNA. The product of this LMNA gene which is a protein i.e. Lamin-A is considered to be responsible for anatomical framing which clasps the nuclei of the cell, well organized and together. But, the recent investigations prove a deformity in the protein i.e. Lamin-A that leads to the non-stability of the nuclei and thus gives rise to the deadly situation of untimely ageing in the children popularly known as Progeria. The literature review investigation provided pivotal information about the therapeutic researches related to the syndrome, the mutational causes and the basic information including the major and minor symptoms generally shown by the patients affected with Hutchinson–Gilford Progeria Syndrome. Investigations on this rare, uncommon disease i.e. Progeria had begun a couple of years back and in some of the researches many important aspects about the causes and possible curative drugs related to the disease which can help the patients in leading a normal life with lesser side effects and symptoms have also been discussed. Further studies will more clearly clarify the possible curative agents and unrevealed mechanisms of the disease which will help the scientists to develop measures which can

provide more beneficial and healthy life to the patients with lesser complications.

Keywords Hutchinson–Gilford Progeria Syndrome · Prelamin-A · Progerin

Introduction

A rare genetic disorder called as Hutchinson–Gilford Progeria Syndrome causes rapid, premature ageing soon after birth. During recent research experiments it was concluded that, a de novo point mutation in the gene named LMNA was basically responsible for this disorder. The premier structural components of the nuclear envelope i.e. Lamin A & C proteins are encoded by LMNA. The site at which the most common HGPS mutation is located is codon 608(G608G). As a result of such type of mutation a splice site is formed within exon number 11, because of which a proteolytic cleavage site gets removed within the expressed mutant Lamin A [1]. This rare disease was independently represented and described by two eminent scientists Jonathan Hutchinson in 1886 and Hastings Gilford in 1897 [2].

Progeria Cases in India

The latest data on Progeria cases as provided by the Progeria Research Foundation indicate that there are about 80 known documented cases of Progeria Syndrome worldwide including 18 in the United States and 4 cases in India. Apart from that, the estimated cases were found to be around 200–250 out of which around 60 are thought to be from India. There have been 4 diagnosed Progeria cases in

✉ Veena Sharma
drvshs@gmail.com

Richa Shukla
rs141294@rediffmail.com

¹ Department of Bioscience and Biotechnology, Banasthali University, Niwai, Tonk, Rajasthan 304022, India

India i.e. Ali Hussain from Bihar, Nihal Bitla from Bhiwandī, 5 years old Aditya from Rajasthan and Prachi from Patna [3].

Symptoms

In the case of Hutchinson-Progeria Syndrome the average age of the child is found to be approximately 13.5 years [4]. The common symptoms related to this disorder include growth retardation, alopecia, atrophy of skin, lipodystrophy, osteolysis and increased perceptivity for malignant tumors [5, 6]. The children afflicted with the disorder appears normal at the time of the birth but in the later stages of their life they show symptoms like weight loss due to growth failure, absence of sexual maturation, abnormal jaw size relative to the size of the head, a high volume voice, lean in appearance with small face, irregular dentition (a phenomena of dental crowding is generally observed) undersized dystrophic clavicles, thin delicate skin [2], high blood pressure, presence of stiff joints, prolonged prothrombin time, high levels of platelet count [7], high levels of urinary excretion of hyaluronic acid, increased amount of low-density lipoproteins and cholesterol levels in the serum are also some of the common symptoms observed in Progeria afflicted individuals [8].

Besides this, some added discoveries including extravagant ocular tearing, Raynaud phenomena, photophobia and exposure keratitis were also observed in few Progeria afflicted individuals which were not common in all the Progeria afflicted individuals [9].

Diagnosis

Despite of the various research activities going on for finding a proper diagnostic method for the disorder, there is no feasible kit available in the market for the accurate initial diagnosis of Hutchinson–Gilford Syndrome. Due to this unavailability of the proper diagnostic kit for the Hutchinson-Progeroid Syndrome, the infant's medical history is basically taken into consideration for the scientific determination along with its physical manifestation. Subsequent to this, in order to start initial curative practices so that the anomaly could get better treatment practice during its initial stages of development, a usual genotypic test involving LMNA alteration is usually carried out, so that a fixed affirmation could be obtained for the syndrome [2].

Cure and Treatment

A scientific test was conducted in the year 2010 under the association Progeria research foundation, National institutes of health, Children's hospital Boston and Dana-Farber cancer institute [10] to evaluate the usefulness of the three "drugs of hope" named as Prevastatin, Lonafarnib and Zoledronic acid for the purpose of finding a cure for Hutchinson-Gilford Progeria Syndrome. Thus, as a result of the test conducted in order to find the cure for the disorder it was reported that the drug, named Lonafarnib was advantageous in curing various cardiovascular conditions related with the syndrome, it helped in bettering bones related disorders and also helped in gaining adiposity to the patients afflicted seriously with the Hutchinson–Gilford Syndrome [11]. Besides Lonafarnib, another drug called as Prevastatin was found helpful in checking cardiovascular problems and was also reported useful in decreasing the cholesterol levels in the body of the Progeria afflicted patients. Along with this, the third drug which also had undergone the scientific test called as Zoledronic acid was reported to be helpful for avoiding bony cracks or wounds by bettering the condition osteoporosis and it was also found to be a biphosphonate type of medicine [10].

Farnesylated Prelamin-A Autophagic Disintegration

Cenni et al. [12] reported that, the phenomena of autophagy could help in the declination of progerin that remains in attachment with the covering of the cell's centre (i.e. the nuclear lamina) in the case of Hutchinson–Gilford Progeria Syndrome. Furthermore, it was also investigated that an accessory reaction of the wild type progerin (i.e. the aggregation of the farnesylated prelamin A) deteriorates the phenotype of the cell [13–15]. Thus, in this case it was reported that, an antibiotic named as rapamycin (associated with the macrolides class) found to trigger the process of autophagy in cells by the disturbance of the distortive path (i.e. the mTOR dependent pathway) could finally result in the stimulation of the process of progerin degeneration [16]. Hence, this particular investigation reveal that when, the Hutchinson-Progeria Syndrome afflicted cells were analysed with antibiotic rapamycin, then it effectively lowered the altitude of prelamin-A as well as progerin, and also stimulated the recovery of trimethylated H3K9 arrangement and hence develops chromatin epigenetic prominence.

Active Chromosome Dynamics and Chromosome Territory Position Restoration by Farnesyltransferase Inhibitor Treatment

Mehta et al. [17] reported that, effective genome mobility as well as chromosome zone location could be re-established by treating the Hutchinson-Progeria Syndrome afflicted cells with farnesyltransferase inhibitor. The enzyme, named farnesyltransferase basically farnesylates the amino acid cysteine, associated with the carboxy-terminal end that contains a motif named as CaaX in the protein called as prelamin-A in the case of normal cells [18]. The attachment of the nuclear sheath with the protein prelamin-A is basically stimulated by the existence of farnesyl group at the carboxy-terminal associated with the CaaX motif and thus, it is very much essential for the precise establishment of the complete protein [19]. But, in the case of Hutchinson–Gilford Progeria Syndrome a splice position located inside the protein Lamin A finally leads to the removal of about 50 amino acids and thus becomes chiefly responsible for the causation of this rare untimely ageing syndrome [20]. But, such kind of removal do not react with the normal farnesylation process of progerin as well as do not pose any kind of negative effect on the CaaX motif. But, such removal process results in loss of ZMPSTE24-FACE1 detection site that was vital for the complete cutting process and thus, as a result, it leaves the progerin in the farnesylated condition [21, 22]. Thus, in the current study performed it was reported that, the medicine called as farnesyltransferase inhibitors (i.e. FTIs) were responsible for the prohibition of the association of the farnesyl group to the protein, as they link in a non-reversible conformation to the CaaX domain [23].

Improvement in DNA Repair and Extension of Lifespan by Depletion of SUV39h1

Baohua et al. [24] studied, enhancement in the reformation of DNA and lengthening of lifetime in a Progeria murine model by reduction in methyltransferase Suv39h1. The investigation carried out in this case presents that, progerin or prelamin-A displays an enhanced linking capability towards SUV39H1 as well as the A-form of lamin protein shows an association with SUV39H1, thus, enhancing the H3K9me3 content by conserving it from the process of proteosomal degeneration. Moreover, reclamation of DNA reconstruction as well as late elderliness in the Hutchinson-Progeria afflicted cells was observed when there was a decreased level of SUV39H1, because as a result of its decreased content the level of H3K9me3 also decreases. An increased agedness in laminopathy established

immature elderliness is the result of adjustment in genome preservation which basically gets stimulated due to increased SUV39h1 constancy in the existence of pre-Lamin A/progerin, which also is responsible for an escalation in the H3K9me3 content. Hence, the current study contributes an interpretation for the epigenetic anomalies observed in the case of Hutchinson-Progeria syndrome, as well as a possible planning for interruption by focusing on heterochromatin redesigning that is generally triggered by SUV39h1.

Prevention of Cancer Invasion and Causation of Progeria by Prelamin-A

Rosa et al. [25] investigated that, prelamin-A is the responsible agent for the causation of Progeria through the cell's outside processes and also prohibits intrusion of cancer. In this case, a mouse model that lacks a metallo-proteinase (i.e. Zmpste 24) which remains altered in the case of Progeria in human beings and also elaborates advancement of prelamin-A present in the nucleus of the cell, reiterates various properties related with Hutchinson–Gilford Progeria Syndrome. But, besides this, their severe anomalies related with the outside and inside of the cell, as well as their smaller lifetime period diminishes the functions as well as explanations of the cancer development procedures. Here, in this case, a mosaic mouse was given that do not represent such obstructions. Thus, the unique zmpste24 mosaic murine considered in this case first of all displayed ordinary progress and also kept analogous magnitude of Zmpste 24 lacking (i.e. prelamin-A aggregating) and Zmpste 24 efficient (i.e. complete Lamin A encompassing) cells all through the lifetime, thus, informing that the outside processes of the cell are dominant for the progression of Progeria Syndrome. Other than this, the aggregation of prelamin-A protein does not diminish the induction or the development of cyst but, it declines the prevalence of penetrating mouth cancer. Besides this, the suppressed Zmpste24 diminishes the incursion of human cancer cells.

Aminopyrimidines: New Regulators of Farnesylation

Blondel et al. [26] investigated, aminopyrimidines as modern regulators of farnesylation, when pharmaceutical examination was conducted on pluripotent stem cells affected with Hutchinson–Gilford Progeria Syndrome. Since, it is a well known fact that, the virulent behaviour of progerin is generally regulated by the process of farnesylation thus, in the current experiment, progression of a

method for the examination of advanced medicinal interrupters for the process of farnesylation was done. Hence, in order to achieve the task, usage of exclusive capabilities of the pluripotent stem cells was done and by such study it was finally concluded that elements like monoaminopyrimidines, usually spot two important biological catalysts i.e. farnesyl transferase and farnesyl pyrophosphate synthase, involved mainly in the farnesylation process. Besides this, it also recovered important physical features through the in vitro analysis, which were mainly linked with Hutchinson–Gilford Progeria Syndrome.

Conclusion and Future Prospects

An uncommonly rare genetic disorder i.e. Hutchinson Gilford Progeria Syndrome causes premature, rapid ageing soon after birth. A de novo point mutation in the LMNA gene was observed in individuals who were diagnosed with the Hutchinson–Gilford Progeria Syndrome. Now this gene LMNA, encodes Lamin A & C, which are the A type lamins, and are premier structural components of the nuclear envelope. Codon 608(G608G), is the site at which the most common Hutchinson Progeria Syndrome mutation is located. A perplexing splice site is thus created by this mutation within exon 11, which as a result removes a proteolytic cleavage site within the expressed mutant Lamin-A. In common terms, an assemblage of fatal, severe, and rare genetic disorders symbolized by various clinical features and phenotypes of physiological ageing prematurely are called as Progeroid-Syndromes.

This rare disease was autonomously represented by and described by two eminent scientists i.e. Jonathan Hutchinson in 1886 and Hastings Gilford in 1897, after which the syndrome name emerged. About one in 4–8 million of new births get affected by Progeria. The prevalence of Progeria is mainly considered as a sporadic disease as it shows no gender- specific, regional or ethnic proclivity.

The basic clinical symptoms of diverse Progeroid Syndromes include retardation of growth, atrophy of skin, alopecia, lipodystrophy, osteolysis & perceptivity for malignant tumors. However, Hutchinson–Gilford Progeria Syndrome afflicted patients remain unaffected in case of the cognitive capabilities. Other than this, a drug named Lonafarnib was found to be advantageous in curing various cardiovascular conditions related with the syndrome, it helped in bettering bones related disorders and also helped in gaining adiposity to the patients affected seriously with the Hutchinson Syndrome as revealed by the information which was gained when a scientific test was organized on approximately 25 children affected with the Progeria Syndrome. Thus, these kinds of results provide astounding

attainment in progressing Progeria related research work that would finally lead to the introduction of a precise cure for such an a new, abnormal and complicated syndrome popularly called as the “Hutchinson–Gilford Progeria Syndrome”. Beside Lonafarnib, other farnesyltransferase inhibitor drugs were also found to be providing quite positive results for the cure of the Progeria Syndrome. In the individuals affected with the Hutchinson Progeria Syndrome, these medicines which were originally advanced as a point medicine for the RAS gene (i.e. oncogenic) helps in inhibiting the enzyme that basically is important for the crucial step of prelamin-A farnesylation. Thus, the usage of such kind of curative therapies as well as the keen interest of researchers in this unique type of syndrome, made this disease a very serious and current topic of research and investigation in the field of life science and thus as a result it opens wide horizons for the scientists associated with different branches of biological science to utilize their potential and knowledge to find out the perfect cure for the syndrome.

Hence, this kind of approach first of all promote more of the scientists towards the field of Progeria research as well as it also provides brilliant opportunities for the young minds to use their capabilities towards finding a cure for a disorder that is very unique on a worldwide basis and can thus prolong the age of those individual affected severely with Progeria.

Compliance with Ethical Standards

Conflict of interest Author A and Author B declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent It is a review article and the article does not contain any such information in the entire manuscript that require any kind of informed consent from any person/participant whatsoever.

References

1. Pollex RL, Hegele RA. Hutchinson–Gilford progeria syndrome. *J Clin Genet*. 2004;66(5):375–81.
2. Sinha JK, Ghosh S, Raghunath M. Progeria: a rare genetic premature ageing disorder. *J Indian J Med Res*. 2014;139(5):667–74.
3. <http://www.itervis.com/progeria-cases-in-india/>
4. Pereira S, Bourgeois P, Navarro C, Esteves-Vieira V, Cau P, De Sandre-Giovannoli A. HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. *J Mech Ageing Dev*. 2008;129:449–59.
5. Hennekam RC. Hutchinson–Gilford progeria syndrome: review of the phenotype. *J Med Genet A*. 2006;40:2603–24.
6. Shalev SA, De Sandre-Giovannoli A, Shani AA, Levy N. An association of Hutchinson–Gilford progeria and malignancy. *J Am J Med Genet A*. 2007;143:1821–6.

7. Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB. Phenotype and course of Hutchinson–Gilford progeria syndrome. *J N Engl J Med*. 2008;358:592–604.
8. Rastogi R, Mohan SMC. Progeria syndrome: a case report. *J Indian J Orthop*. 2008;42:97–9.
9. Gordon LB, Brown WT, Collins FS. Hutchinson–Gilford progeria syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle: University of Washington; 2003.
10. Gordon LB, Massaro J, D’Agostino RB, Campbell SE, Brazier J, Brown WT. Impact of farnesylation inhibitors on survival in Hutchinson–Gilford progeria syndrome. *J Circ*. 2014;130(1):27–34.
11. Gordon LB, Kleinman ME, Miller DT, Neuberg DS, Giobbie-Hurder A, Gerhard-Herman M. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome. *J Proc Natl Acad Sci USA*. 2012;109:16666–71.
12. Cenni C, Capanni M, Columbaro M, Ortolani MR, D’Apice G, Novelli M, et al. Autophagic degradation of farnesylated prelamin A as a therapeutic approach to lamin-linked progeria. *Eur J Histochem*. 2011;55(4):e36.
13. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. *J Proc Natl Acad Sci USA*. 2004;101:8963–8.
14. Capanni C, Cenni V, Haraguchi T, Squarzoni S, Schuchner S, Ogris E. Lamin A precursor induces barrier-to-autointegration factor nuclear localization. *J Cell Cycle*. 2010;9:2598–608.
15. Haque F, Mazzeo D, Patel JT, Smallwood DT, Ellis JA, Shanahan CM. Mammalian SUN protein interaction networks at the inner nuclear membrane and their role in laminopathy disease processes. *J Biol Chem*. 2010;285:3487–98.
16. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *J Nat*. 2009;460:392–5.
17. Mehta IS, Eskiw CH, Arican HD, Kill IR, Bridger JM. Farnesyltransferase inhibitor treatment restores chromosome territory positions and active chromosome dynamics in Hutchinson–Gilford progeria syndrome cells. *J Genome Biol*. 2011;12(8):R74.
18. Beck LA, Hosick TJ, Sinensky M. Isoprenylation is required for the processing of the lamin A precursor. *J Cell Biol*. 1990;110:1489–99.
19. Hennekes H, Nigg EA. The role of isoprenylation in membrane attachment of nuclear lamins. A single point mutation prevents proteolytic cleavage of the lamin A precursor and confers membrane binding properties. *J Cell Sci*. 1994;107:1019–29.
20. Kelley JB, Datta S, Snow CJ, Chatterjee M, Ni L, Spencer A, et al. The defective nuclear Lamina in Hutchinson–Gilford progeria syndrome disrupts the nucleocytoplasmic ran gradient and inhibits nuclear localization of Ubc9. *J Mol Cell Biol*. 2011;31(16):3378–95.
21. Eriksson M. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. *J Nat*. 2003;423:293–8.
22. Fong LG, Ng JK, Meta M, Coté N, Yang SH, Stewart CL, et al. Heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24-deficient mice. *J Proc Natl Acad Sci USA*. 2004;101:18111–6.
23. Adjei AA. Farnesyltransferase inhibitors. *Cancer Chemother Biol Response Modif*. 2005;22:123–33.
24. Liu B, Wang Z, Zhang L, Ghosh S, Zheng H, Zhou Z. Depleting the methyltransferase Suv39h1 improves DNA repair and extends lifespan in a progeria mouse model. *Nat Commun*. 2013;4:1868.
25. Rosa JDL, Freije JMP, Cabanillas R, Osorio FG, Fraga MF, Soledad Fernández-García M, et al. Prelamin A causes progeria through cell-extrinsic mechanisms and prevents cancer invasion. *J Nat Commun*. 2013;4:2268.
26. Blondel S, Egesipe AL, Picardi P, Jaskowiak AL, Notarnicola M, Ragot J, et al. Drug screening on Hutchinson Gilford progeria pluripotent stem cells reveals aminopyrimidines as new modulators of farnesylation. *Cell Death Dis*. 2016;7(2):e2105.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.