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Mini Review

Hutchinson–Gilford progeria syndrome

Pollex RL, Hegele RA. Hutchinson–Gilford progeria syndrome.
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Hutchinson–Gilford progeria syndrome (HGPS) is an extremely rare genetic disorder that causes premature, rapid aging shortly after birth. Recently, *de novo* point mutations in the *Lmna* gene have been found in individuals with HGPS. *Lmna* encodes lamin A and C, the A-type lamins, which are an important structural component of the nuclear envelope. The most common HGPS mutation is located at codon 608 (G608G). This mutation creates a cryptic splice site within exon 11, which deletes a proteolytic cleavage site within the expressed mutant lamin A. Incomplete processing of prelamin A results in nuclear lamina abnormalities that can be observed in immunofluorescent studies of HGPS cells. Mouse models, such as *Lmna* knockout, *Zmpste24* knockout, and *Lmna* L530P knockin will help the study of progeria. *Lmna* mutations have also recently been found in patients with atypical forms of progeria. The discovery of the HGPS mutations brings the total number of diseases caused by mutant *Lmna* to nine, underscoring the astonishing spectrum of laminopathies. Future research into HGPS could also provide important clues about the general process of aging and aging-related diseases.

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Hutchinson–Gilford progeria syndrome (HGPS; MIM 176670), a rare genetic disorder associated with a characteristic aged appearance very early in life, was originally described more than 100 years ago (1, 2). The syndrome was given the name progeria (from the Greek, gēras, meaning old age) 'in recognition of the senile characters which form such a conspicuous feature of the disease from the beginning' (1). The reported incidence of HGPS is 1 in 8 million, though the true figure might be closer to 1 in 4 million, taking into consideration unreported or misdiagnosed cases. Since 1886, just over 100 cases of HGPS have been reported and currently there are approximately 40 known cases worldwide (www.hgps.net).

Clinical features

Children born with HGPS typically appear normal at birth, but within a year they begin to display the effects of accelerated aging (Fig. 1). Typical facial features include micrognathia (small jaw), craniofacial disproportion, alopecia (loss of hair), and prominent eyes and scalp veins. Children experience delayed growth and are short in stature and below average weight. Due to a lack of subcutaneous fat, skin appears wrinkled and aged looking. Other key abnormalities include delayed dentition, a thin and high pitched voice, a pyriform (pear-shaped) thorax, and a 'horse riding' stance (3). As they mature, the disorder causes children to age about a decade for every year of their life. This means that by the age of 10, an affected child would have the same respiratory, cardiovascular, and arthritic conditions as a senior citizen (4). On average, death occurs at the age of 13, with at least 90% of HGPS subjects dying from progressive atherosclerosis of the coronary and cerebrovascular arteries (5).

Inheritance of HGPS

Hutchinson–Gilford progeria syndrome had been proposed to be a recessive disorder due to observations of affected individuals found in consanguineous families (6–8). However, many cases of progeria were also observed in families in which the parents were not related, suggesting sporadic autosomal dominant inheritance (9), which has been confirmed with the discovery of the causative mutations. Others have reported the presence of various chromosomal abnormalities, such as

Fig. 1. Photograph of two boys diagnosed with Hutchinson–Gilford progeria, ages 6 and 15 years. Courtesy of The Progeria Research Foundation.

an inverted insertion in the long arm of chromosome 1 (10) and an interstitial deletion of chromosome 1q23 (11), as possible contributing factors to the disease. These cytogenetic clues proved to be critical for discovery of the HGPS gene.

The search for the HGPS gene

After many years of appreciating that HGPS was caused by genetic rather than by environmental factors, researchers took the first steps in isolating genetic mutations that cause HGPS. A team centered at the National Human Genome Research Institute in Maryland, under the direction of Francis Collins, initiated their search with a genome-wide scan (12). Using 403 polymorphic microsatellite markers, the investigators found no evidence of homozygosity in 12 individuals with classical HGPS. However, two individuals showed uniparental isodisomy of chromosome 1q, and one had a 6 Mb paternal interstitial deletion in 1q. From this observation, the investigators concluded that the HGPS gene must lie within a 4.82 Mb region on chromosome 1q. This region contains approximately 80 known genes, including *Lmna*.

Lmna

A-type and B-type lamins (Type V intermediate filaments) are the main components of the nuclear lamina, the innermost layer of the nuclear envelope. The nuclear lamina in mammalian cells is a thin (20–50 nm) protein meshwork that interacts with various proteins and chromatin and is essential for maintaining the structural integrity of the nuclear envelope, the protective barrier between the cytoplasm and nucleus (13).

The A-type lamins are encoded by *Lmna* (MIM 150330), which spans 57.6 kb of genomic DNA. By alternative splicing of its 12 exons, four proteins are created: two minor products: lamin AΔ10 and lamin C2; two major products: lamin A and lamin C. Lamin A is coded for by exons 1–12 and lamin C is derived from *Lmna* by use of an alternative splice site in intron 10. Thus, lamin C differs at the C-terminal from lamin A, since it lacks the final part of exon 10, as well as exons 11 and 12 (14). Lamin A, a 664 amino acid protein with a molecular weight of 70 kDa, is normally synthesized as a precursor molecule, called prelamin A. It contains a CAAX-box motif at the C-terminus, which is subject to farnesylation. After farnesylation, an internal proteolytic cleavage occurs, removing the last 18 coding amino acids to generate mature lamin A (15). Lamin C is slightly smaller with a length of 574 amino acids and a weight of 65 kDa. Together, the two proteins form heterodimers through their rod domains, to create the filamentous structures found in the nuclear lamina (16).

Discovery of *Lmna* mutations in HGPS

Reasoning that *Lmna* was a good candidate due to its involvement in a number of heritable disorders, Collins and his team decided to screen 23 affected individuals for mutations. Their gamble paid off. Three different *de novo* mutations in *Lmna* were found: G608G (GGC > GGT), G608S (GGC > AGC), and E145K (GAG > AAG) (Fig. 2). In all the cases, the affected individuals carried only one mutation and were

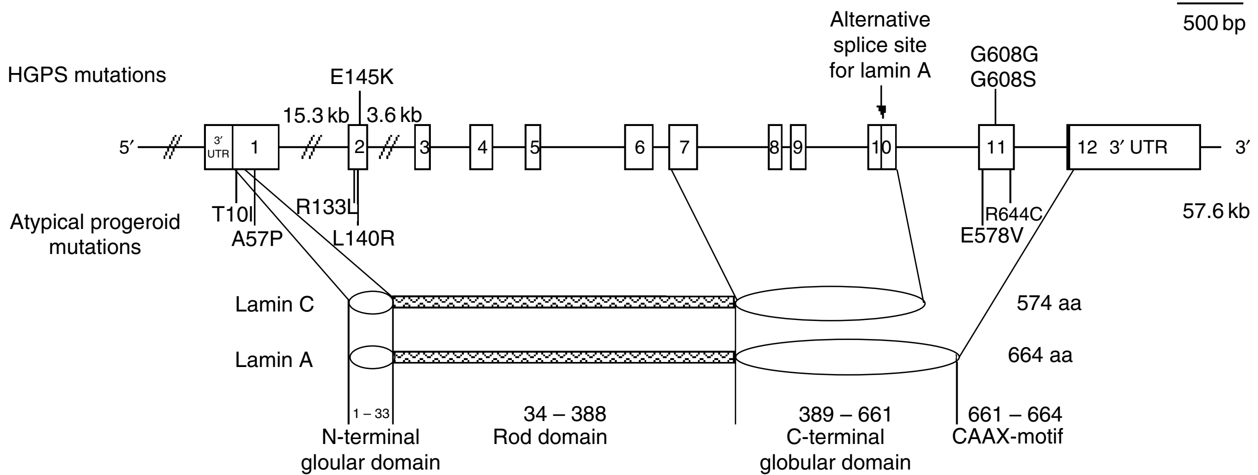

Fig. 2. Schematic representation of *LMNA* genomic structure, mutations, and the lamin A and C protein isoforms. Scale is shown in upper right section of figure. Above the *LMNA* gene are shown the names and positions of mutations found in patients with typical Hutchinson–Gilford progeria syndrome. Position of the alternative splice site in exon 10 giving rise to lamin A and C isoforms is shown. Lengths of intron 1 and intron 2 are not to scale. Below the *LMNA* gene are shown the names and positions of mutations found in patients with atypical progeroid syndromes. Bottom half of the figure shows the lamin C and A isoforms, functional domains, number of amino acid residues per domain, and mapping to the respective genomic DNA sequences that give rise to these domains (modified from (37)).

heterozygous for this novel base substitution. The silent G608G mutation was the most frequent, occurring in 18 of the 23 probands. G608S and E145K were both found as unique substitutions in one patient each. E145K was found in a patient who had atypical clinical features that may distinguish the phenotype from classical HGPS. The remaining three individuals who had no *Lmna* mutations had either uniparental isodisomy or a large paternal chromosomal deletion.

Similarly, on-going research led by Nicolas Levy at INSERM in Marseille, France, discovered the same unique heterozygous C > T substitution at *Lmna* codon 608 in two HGPS patients (17). They showed the possible effect of this silent mutation on transcript splicing.

At the same time, Cao and Hegele (18) at the Robarts Research Institute in London, Ontario, were searching for causative mutations for progeroid syndromes. They screened cell lines from HGPS individuals for mutations in *Lmna* in part because of their longstanding interest in this gene. In retrospect, *Lmna* was an excellent candidate gene based on the evidence that patients with progeria had a lipodystrophy-like phenotype similar to those with mandibuloacral dysplasia (MAD; MIM 248370) with partial lipodystrophy, which previously had been shown to be due to mutations in *Lmna* (19). Cell lines from two patients with Wiedemann–Rautenstrauch progeroid syndrome (WRS; MIM 264090), a severe progeroid syndrome with lipodystrophy as a clinical feature, were also included in the study. By screening genomic DNA from seven individuals with HGPS, Cao and Hegele confirmed the presence of both the G608S and G608G (GGC > GGT) mutations occurring as simple heterozygotes. No *Lmna* mutations were found in the two patients with WRS. Compound heterozygosity for two *Lmna* mutations (R471C, R527C) was identified in the cell line of a patient who reportedly had an apparently typical phenotype, but at age 28, was much older than typical HGPS probands. Interestingly, this patient has recently been reclassified by her physician as having MAD rather then HGPS (MIM 150330.0025).

Codon 527 appears to be a site of 'codon heterogeneity', as a total of three different substitutions have now been documented at this codon. In addition to the R527C mutation, a homozygous R527H mutation was found in another individual with MAD (19), and R527P was found in a patient with autosomal dominant Emery–Dreifuss muscular dystrophy (EDMD; MIM 310300) (20). It is quite remarkable that both EDMD and MAD can arise from the alteration of a single amino acid in lamin A/C, albeit with different substitutions yielding different tissue involvement.

Assuming that these cases are indeed *de novo* point mutations in *Lmna*, is it not notable that 90% of HGPS subjects have the same C > T substitution at codon 608? The substitution occurs at a highly mutable CpG dinucleotide, as a methylated C can be deaminated to T and miscopied. Thus, it is very likely that codon 608 is simply a 'hotspot' for recurring point mutations occurring on different genetic backgrounds. Furthermore,

among four individuals studied by Eriksson et al. (12), the C > T mutation occurred on the paternal allele, while other individuals were not informative (21). A recent study of three families with an HGPS-affected child similarly showed that the *de novo* G608G mutation occurred on the paternal *Lmna* allele. A similar phenomenon has previously been observed in other genetic diseases such as achondroplasia, Apert syndrome, Crouzon syndrome, and Pfeiffer syndrome, in which most appeared to be sporadic cases due to mutations occurring on the paternal allele (22–24). Like HGPS (21), many of these other disorders are associated with advanced paternal age. It has been hypothesized that increased paternal age may lead to an increased frequency of mutant sperm; however, at least for achondroplasia, this theory has been disproved (25).

HGPS mutation *Lmna* G608G activates a cryptic splice site

How can these silent, conservative *de novo* mutations cause such a devastating phenotype? It appears that the mutations at codon 608 improve the match to a splice site: G|GT(A/G)AGT. The activation of this cryptic splice site would result in the splicing of the transcript within exon 11, effectively removing 150 nucleotides from the end of exon 11 before exon 12 sequence begins to be translated (Fig. 3). With the reading frame

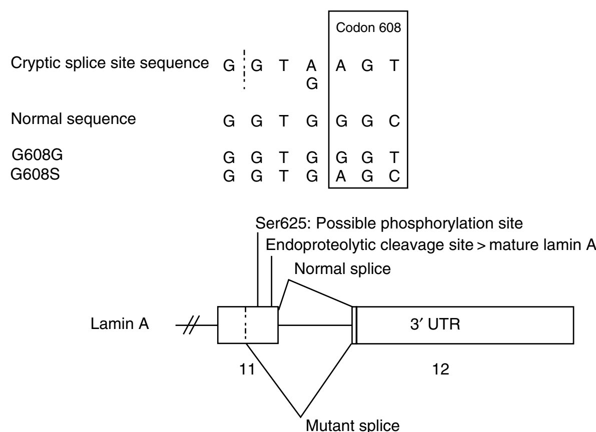

Fig. 3. Schematic representation of the cryptic splice site and alternative splicing products. Top line shows consensus nucleotide sequence for RNA splicing. Normal *LMNA* nucleotide sequence is shown in the next line. Sequences for G608G and G608S mutations are shown below that. Codon 608 sequence is enclosed in a box. The schematic diagram in the lower part of the figure shows the positions of donor and acceptor nucleotides for normally spliced *LMNA* and for the *LMNA* allele containing the cryptic splice site created by the Hutchinson–Gilford progeria syndrome mutations. Potentially important functional residues such as the putative phosphorylation site at Ser625 and the endoproteolytic cleavage domain are also shown (Modified from (12)).

maintained, the final mutant protein would be expected to have an internal deletion of 50 amino acids near the C-terminus of lamin A, as confirmed by reverse transcription-polymerase chain reaction and Western blot analysis (12, 17).

With the activation of the cryptic splice site within exon 11, lamin A would be translated with an internal deletion (pVal607-Gln656del). The prelamin A would retain the CAAX-box, allowing for farnesylation, while lacking the site for internal proteolytic cleavage. In addition, a potential phosphorylation site at Ser625 would also be deleted (12). Without the complete processing of the prelamin A and the deletion of a potential phosphorylation site, the resulting mutant lamin A might be expected to interact aberrantly with lamin C when creating heterodimeric multiprotein filaments, and would thus act as dominant negative (12). Without the proper structural components in the nuclear lamina, there is potential for great nuclear instability. This instability could possibly lead to the process of premature aging in progeria.

Cell studies of HGPS patients

Immunofluorescence studies with antibodies against lamin A/C were performed using fibroblasts from HGPS subjects and their parents. The results showed structural nuclear abnormalities in 48% of HGPS cells compared with <6% of normal control cells (12). Additional analyses described HGPS lymphocytes as having 'strikingly altered nuclear sizes and shapes, with envelope interruptions accompanied by chromatin extrusion' (17). Lamin A expression in HGPS lymphocytes was only 25% of that from normal controls (17). In more recent studies, Bridger and Kill (26) have observed that HGPS fibroblasts undergo a period of hyperproliferation followed by rapid apoptotic death. These experiments are starting to clarify cellular processes in premature aging due to mutant *Lmna*.

Mouse studies

Three different mouse models have begun to shed some light on HGPS pathogenicity. Each model supports the link between *Lmna* and progeria. An *Lmna* knockout mouse by Sullivan et al. (27) resulted in a mouse that had severe postnatal growth delays, muscular dystrophy, and nuclear abnormalities. In 2002, Bergo et al. developed a mouse knockout of the *Zmptse24* metalloproteinase, an enzyme thought to be involved in the proteolytic processing of prelamin A (28). The

knockout mice had an HGPS-like phenotype, complete with growth retardation, premature death from cardiac dysfunction, alopecia, and nuclear abnormalities. Lastly, knockin mice carrying an autosomal recessive mutation (L530P) in *Lmna* displayed a reduction in growth rate, death by 4 weeks of age, and other progeroid abnormalities of the bone, muscle, and skin (29). More recent studies with lamin A/C-deficient mice have defined some of the potential disease mechanisms. In monocytes from lamin A/C-deficient mice, Nikolova et al. (30) observed both the central displacement and fragmentation of heterochromatin, which could play a role in altered gene transcription, as well as the disorganization and detachment of desmin filaments, which could impair nuclear pore transport. In studying the effects of mechanical strain on fibroblasts of lamin A/C-deficient mice, Lammerding et al. (31) noted increased nuclear fragility and altered gene transcription. Worman and Courvalin (32) commented on these findings and concluded that the general disease mechanism for *Lmna* mutations follows a two-stage process (1): mechanical defects of the nucleus (2), abnormal interactions with transcription factors, and abnormal regulation of gene expression. Together, these models will provide researchers with another avenue for seeking answers to the molecular mechanisms of aging.

Lmna mutations in atypical progeroid patients

Werner's syndrome (WRN; MIM 277700) is another progeroid syndrome. Later onset, skin calcification, cataracts, and cancer susceptibility are a few of the features that distinguish it from HGPS (33). Mutations for this disease have been found in the *WRN* gene which encodes WRN protein, a member of the RecQ family of DNA helicases (34). However, not all individuals diagnosed with WRN carry a mutation in *WRN*. A subset of these atypical WRN patients, with an earlier mean age of diagnosis than the classical WRN, were shown to actually carry novel mutations in *Lmna*, namely A57P within the globular head domain and R133L and L140R, both within the alpha-helical coiled coil domain (35). The diagnosis of these younger WRN patients as having a laminopathic progeria would suggest that they might actually be atypical HGPS rather than atypical WRN. In a recent screening of atypical progeroid patients, three additional novel heterozygous *Lmna* mutations have been found, namely, R644C affecting the C-terminus in a subject with atypical HGPS, E578V also in the C-terminus in a subject with either severe WRN or mild HGPS, and T10I within the N-terminal globular domain in a patient diagnosed with Seip syndrome (36). Fibroblasts from these probands contained a large proportion of irregularly shaped nuclei as observed previously in other laminopathies (36). Hence, *Lmna* is a good candidate not only for HGPS, but also for atypical progeria. Such findings indicate that molecular diagnosis can help classify subjects with ambiguous or unclear clinical diagnosis. Future treatments may depend on having a precise molecular diagnosis.

Allelic heterogeneity

A plethora of mutations has been identified within *Lmna*, making HGPS and atypical progerias just one of at least nine genetic disorders associated with this gene (37). The other disorders include various forms of different striated muscle diseases such as autosomal and recessive forms of Emery–Dreifuss muscular dystrophy (AD/AR-EDMD) (20, 38), dilated cardiomyopathy type 1A (CMD1A) (39), and limb–girdle muscular dystrophy type 1B (LGMD1B) (40). Autosomal recessive axonal Charcot–Marie–Tooth disease (AR-CMT2) (41), a peripheral neuropathy, is also associated with *Lmna*, as are partial lipodystrophy syndromes such as Dunnigan type familial partial lipodystrophy (FPLD) (42), the syndrome of lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis and cardiomyopathy (LIRLLC) (43), and MAD (19). Muscle, fat and bone cells all derive from mesenchymal cells, indicating that perhaps the lamins play an important role in the development, maintenance, or repair of this cell line. Having so many distinct phenotypes arising from a simple gene supports the idea that lamins have multiple functions within the nuclear envelope (32, 37).

Difficulties underlying HGPS research

The recent discovery of *Lmna* mutations in HGPS provides hope both for the children affected by this disease and for their families. However, a cure is still in the distant future, with much work needed to determine the detailed cellular mechanisms underlying the disease. There are many obstacles hindering the investigation of HGPS. A major hurdle is the small number of individuals affected with HGPS: <40 known cases worldwide at present. The Coriell Cell Repository and the Progeria Research Foundation Cell and Tissue Bank are excellent resources,

but still, the numbers of affected subjects are few. In addition, many patients do not have a typical phenotype. There may also be other genetic loci that can modify the HGPS phenotype. Other challenges will lie in determining the most appropriate mouse models. For example, how suitable is the *Lmna*$^{L530P/L530P}$ progeria mouse model, considering that it shows no evidence of having atherosclerotic disease, which is a major component of human HGPS?

Molecular diagnostics

As most cases of HGPS appear to be due to a *de novo* mutation in the same codon (G608G), screening for this mutation is certainly theoretically feasible, especially with the decreasing cost of genomic DNA analysis. However, due to the sporadic nature of the phenotype, predictive screening is not practical at present, since there is no way to determine which children are at risk. Furthermore, the benefit is limited, considering that there is no present treatment for progeria. For the parents of a previously affected child, parental somatic mosaicism is a theoretical possibility. Concerns about the recurrence of HGPS in future pregnancies for such individuals might now be addressed through genetic testing. *Lmna* testing may also be valuable in making a molecular diagnosis in an individual affected with a suggestive phenotype, that is, to determine whether their disease was 'classical' HGPS or atypical progeroid. As mentioned above, a precise molecular diagnosis may be important, as future therapies may depend upon knowing the genetic basis of the phenotype.

New insights for cardiovascular research and the aging process

Some of our current understanding of cardiovascular disease susceptibility arose from the study of rare monogenic metabolic diseases with extreme phenotypes such as familial hypercholesterolemia (MIM 151660) (44), Tangier disease (MIM 205400) (45), and abetalipoproteinemia (MIM 200100) (46). Hutchinson–Gilford progeria syndrome now represents a unique opportunity to study the disease process of atherosclerosis from a different angle. For instance, the proteins that bind abnormally to mutant *Lmna* in HGPS (47) may also play a pathogenic role in common atherosclerosis. Typically, common atherosclerosis is heavily influenced by environment and generally takes decades to develop, making it difficult to study the progression and development of this disease. However, HGPS patients develop atherosclerosis at an accelerated rate, apparently with little environmental stress, suggesting that molecular mechanisms predominate. Detailed study of HGPS and *Lmna* mutations may also advance our understanding of the process of aging. Why do *Lmna* mutant cells enter senescence earlier than normal cells? Some consider that the answers to this question may provide the key for the 'fountain of youth' or the 'elixir of life'. But, do we really want to open that door?

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