Hutchinson-Gilford Progeria Syndrome
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Hutchinson-Gilford progeria syndrome (HGPS, progeria) is an extremely rare monogenic disorder in which children display signs of premature, rapid aging very early in life (1). It is defined by the presence of a recurrent de novo G608G mutation in exon 11 of the Lmna gene (2). The aging process in individuals with HGPS is said to be accelerated by about seven times the normal rate, which would result in a ten-year-old child having the respiratory, cardiovascular, and arthritic symptoms characteristic of a seventy-year-old adult (3). The reported incidence of this disorder is 1 in 8 million, but could be as high as 1 in 4 million, which takes into consideration unreported or misdiagnosed cases. To date, there have been just over 100 known cases worldwide, approximately forty of which are current. People affected with HGPS tend not to live beyond their teenage years, with cause of death predominantly due to atherosclerosis (1).

Children with HGPS typically appear normal at birth, but then experience severe failure to thrive during the first year of life (2). Diagnosis of the disorder is based on both recognition of common clinical manifestations and identification of the Lmna G608G mutation. Certain abnormalities are almost always present in these children after the age of three including delayed growth, short stature, and below-average weight. Children with HGPS also display typical facial features such as a small jaw, prominent eyes, hair loss, craniofacial disproportion, delayed and crowded dentition, and prominent scalp veins. Because they usually have diminished subcutaneous fat, their skin appears wrinkled and aged. Other abnormalities include a thin, high-pitched voice, a pear-shaped thorax, a “horse-riding” stance, and stiff joints. Most debilitating, however, are the effects of this disease on the child’s cardiovascular system. HGPS causes severe, progressive atherosclerosis that results in heart attacks or strokes. Children with HGPS experience normal motor and mental development (1, 2).

Since HGPS is defined by the presence of the Lmna G608G mutation, diagnosis can be confirmed with molecular genetic testing. Specifically, either sequence analysis (analysis of the entire coding region) or targeted mutation analysis can be used to detect the Lmna G608G point mutation, with a 100% detection rate. Seven laboratories in the United States and one in
Switzerland are listed on the GeneTests website as offering clinical testing for progerid laminopathies, of which HGPS is a subset (2).

At the present time, there is no treatment for Hutchinson-Gilford progeria syndrome. There are, however, several recommendations for management of the various symptoms associated with this disorder. At the initial diagnosis, the patient’s vascular status, bone mineral density, and global joint mobility should be evaluated to establish the extent of the disease. Patients should maintain a regular diet unless their lipid profile becomes abnormal, at which time exercise, modifications in diet, and medication are recommended. Before they experience decline in cardiovascular or neurologic status, children with HGPS should be encouraged to be physically active, although they must be careful because they are especially susceptible to fractures and hip dislocation. Routine physical and occupational therapy are recommended to maintain joint mobility (2).

Sadly, prognosis for individuals with HGPS is poor, as the disorder is associated with a very short life span. Children affected with the disease usually die between the ages of six and 20, with an average life span of 13 years. Approximately 90% of patients with HGPS die from progressive atherosclerosis of coronary and cerebrovascular arteries (1).

Previous thought proposed HGPS to be an autosomal recessive disorder, due to the observation that affected individuals were from consanguineous families. Recent findings, however, suggest an autosomal dominant pattern of inheritance, with most cases arising from a new mutation. To isolate the gene or genes involved in the disease, researchers used polymorphic microsatellite markers from 12 affected individuals to scan for commonalities between them. This study led to the correlation of the \textit{Lmna} gene, which lies on chromosome 1q, with progeroid diseases. None of the individuals studied showed homozygosity at this locus, expelling the notion of autosomal recessive inheritance. Three individuals did show variation in the \textit{Lmna} gene; two patients showed uniparental isodisomy, which is defined as the inheritance of two of the same parental chromosomes, and one patient showed a paternal deletion in 1q. In a later study involving 23 of the approximately 40 affected individuals, three \textit{de novo} mutations were found: G608G, G608S, and E145K. The most frequently observed mutation (seen in 18/23 individuals) was G608G, while the other two were observed in one patient each. In the three patients with no \textit{Lmna} mutation, either uniparental isodisomy or paternal deletion was observed (1). In all cases, however, affected individuals carried just one mutation, rather than the two that would be required for a recessive phenotype to manifest itself.

The \textit{Lmna} gene, which is 57.6 Kb long, codes for a protein called Lamin A, which, together with Lamin C, forms the protein meshwork of the nuclear lamina. This nuclear lamina interacts with proteins and chromatin, and is essential for maintaining the structure of the nuclear envelope. Four protein products are produced by the \textit{Lmna} gene, via alternative splicing. Interestingly, it has been found that 90% of HGPS subjects have the same C to T substitution at codon 608, which contains a CpG dinucleotide that could be deaminated to T. This substitution also seems to occur more frequently on the paternal allele, indicating that HGPS may be associated with advanced paternal age as increased paternal age could lead to an increased incidence of mutant sperm.

The mechanism by which a mutation at codon 608 produces such a drastic phenotype is still not well understood, but it appears that the mutation converts the codon into a splice site, which results in splicing at exon 11. This splicing removes the 150 nucleotides that follow this codon on exon 11, which removes 50 amino acids from the Lamin A protein. The protein retains most of the structural components that allow for post-translational modification into prelamin A,
such as a carboxy terminus -CAAX motif that allows for farnesylation, a key step in the maturation of the protein. However, the deletion results in the loss of an internal proteolytic cleavage site and a potential phosphorylation site, which impedes Lamin A processing into mature Lamin A and alters its interaction with Lamin C when forming heterodimers (4).

Due to the strong correlation between HGPS and the G608G mutation on the Lmna gene, prenatal screening for this mutation is certainly a plausible option, but is usually only recommended for families who have an affected member, as there is a risk of recurrence of one in five hundred (2). It would not be recommended as a general screening tool, however, for various reasons. The phenotype of progeroid diseases, for example, is difficult to predict, so there is no way to know which children are at risk. No one ethnic group is known to be more susceptible than another and the disease is rare enough that general screening would be a waste of resources. Also, screening could be only minimally beneficial as there is currently no treatment for HGPS.

As mentioned above, the Lmna gene encodes A-type lamins, lamin A and C, which are needed to maintain the structural integrity of the nuclear envelope. Point mutations in the Lmna gene are the key cause of Hutchinson-Gilford progeria syndrome (HGPS). Previously discussed, the mutation is a splice site mutation that eliminates a proteolytic cleavage site from the lamin A protein. Thus, the mutant lamin A is incompletely processed after translation and is expected to erroneously interact with lamin C. Normally, lamin A and lamin C interact to form a heterodimeric multiprotein filament, namely intermediate filament, that contributes to the structure and stability of the nuclear membrane (1). Intermediate filaments are the predominant structural component of the nuclear lamina, which is the filamentous meshwork constituting the innermost layer of the nuclear membrane (5). The nuclear lamina is involved in many nuclear activities such as DNA replication, nuclear and chromatin organization, nuclear stability, cell cycle regulation, cell development, and apoptosis. Without normal filamentous proteins, cell nuclei do not behave properly. Problems with the nuclear lamina would cause problems in all the aforementioned cell functions and these problems are related to the phenotype seen in HGPS, as will be discussed (6).

Lamin A, as well as other lamin proteins, contains an amino-terminal globular domain, a central helical rod domain, and a carboxy-terminal globular domain. Producing mature lamin A is a complex process involving four steps. First, a 15-carbon farnesyl lipid is added to a cysteine of lamin A. Second, the –aaX motif of its terminal –CaaX motif is taken off. Third, the farnesyl group is carboxy-methylated and lastly, the farnesylcysteine methyl ester is clipped off and degraded to make mature lamin A. Young, et al. postulate that the farnesylcysteine methyl ester helps to target prelamin A to the nuclear envelope where the final step occurs to produce mature lamin A. As mentioned above, mature lamin A and C then form a heterodimeric multiprotein filament which associate head to tail and then interact laterally to form higher-order filaments. These higher-order filaments form the nuclear lamina of the inner nuclear membrane. In HGPS, the splice site mutation removes the proteolytic cleavage site that normally leads to the removal of the farnesyl group from Lamin A. The result is farnesyl-prelamin A accumulating in the nuclear envelope causing deformed cell nuclei leading to nuclear abnormalities that are likely related to the premature aging seen in HGPS (5). For example, with a compromised nuclear lamina matrix, nuclei are affected by mechanical stress. One can relate this to an increased fragility of nuclei in blood vessel walls, thus causing the severe atherosclerosis usually seen in HGPS patients (7). Cells without the Lmna gene (Lmna-/-) demonstrate cell pathologies that are likely related to premature and advanced aging seen in HGPS. For example, Lmna-/- fibroblast
cells are more apoptotic than normal fibroblasts. Recall that the nuclear lamina is involved in normal apoptosis so without lamin proteins the cell undergoes erroneous apoptosis. Fibroblast cell death can be related to the wrinkled appearance of the skin of HGPS patients (1, 5). A disrupted nuclear lamina leads to myriad cellular problems which cause HGPS.

Recent studies have given clues for potential treatment in HGPS. One study blocked farnesylation of Prelamin A, as to localize Prelamin A away from the nuclear envelope and reduce cells with deformed nuclei. In fact, there was a reduced percentage of mishappen cell nuclei. Farnesyl transferase inhibition also showed improved nuclear shape in mouse fibroblasts. This hints that farnesylated prelamin A is the culprit and therapeutic target of HGPS. Interestingly, a mouse with mutant \textit{Lmna} gene that only produced farnesylated Prelamin A exhibited a phenotype similar to human HGPS patients, which included retarded growth, reduced adipose tissue, and osteoporosis. Furthermore, farnesyl transferase inhibitors improved the survival of mice missing the enzyme, \textit{Zmpste}, which is responsible for the cleavage events producing mature lamin A (5).

Farnesyl inhibition is currently being studied as a potential method of treatment of HGPS. Indeed, issues arise with nonfarnesylated prelamin A potentially causing toxicity in the cell, just as farnesylated prelamin A does (5). These issues are currently being investigated and farnesyl inhibition is potential treatment route in HGPS.

Although Hutchinson-Gilford progeria syndrome is an extremely rare genetic disease, it has devastating effects on affected individuals and their families. Currently, there is no cure for HGPS and children tend not to survive past the age of thirteen. Research has been hindered by the small number of people affected by HGPS and the heterogeneity in phenotype. However, future research in farnesyl transferase inhibition provides a hopeful outlook for eventual therapeutic interventions.

References
2. www.genetests.org
3. www.hgps.net