Hutchinson-Gilford Progeria Syndrome or HGPS is a rare genetic disorder characterized by the premature development of aging-like phenotypes. It occurs in one in four million births independent of ethnic background. It is caused by a de novo dominant mutation (G608G) in exon 11 of the LMNA gene and is 100% penetrant. This results in the accumulation of a mutant farnesyl-prelamin A protein that disrupts the structural scaffolding for the cell nucleus, leading to misshapen nuclei. Individuals affected with the disease have a multitude of symptoms ranging from alopecia to osteoporosis although they have normal motor and mental function. Children with HGPS will eventually develop severe atherosclerosis and death via cardiac complications occurs before 20 years of age [1].

Genetics, Biochemistry and Molecular Biology of HGPS

HGPS is caused by a de novo mutation of the LMNA (Lamin A/C) gene, which is approximately 24 kilobases long and contains 12 exons. In normal individuals, the LMNA gene encodes for lamins A and C, two of the major components of the nuclear lamina, which is a protein-containing layer attached to the inner nuclear membrane of various cells throughout the body that acts as a scaffold for the cell nucleus. These two proteins are formed by alternative splicing within exon 10 of the lamin A/C gene. The other two major components of the nuclear lamina family of proteins are lamins B1 and B2; however those are made by a separate gene. [1]

Each of the proteins within this family has similar structural domains. For example, they each contain an N-terminal head domain, an alpha-helical rod domain, which is essential for dimerization, and a globular C-terminal tail domain. This family of proteins is extremely important to the cell due to the numerous and widespread functions of each of the specific proteins. “They can be regarded as the main determinants of the nuclear architecture [in that] they give the nuclear envelope its mechanical strength, determine the nuclear shape [and] nuclear pore complexes, and form the structure in which many other proteins anchor.” [2] Due to their location at the nuclear membrane in the cells, they play a pivotal role in DNA replication, mRNA transcription, and participate in gene regulation and a number of signal transduction pathways.

LMNA normally encodes for prelamin A, which is a precursor molecule to the lamin A protein. Prelamin A undergoes posttranslational modifications involving a number of steps. A CaaX motif exists at the C-terminal end of the prelamin A gene product. This stands for a cysteine residue followed by two aliphatic residues, or containing acyclic carbon compounds, followed by any other residue. The presence of this motif allows the protein farnesyltransferase to farnesylate (add oily hydrocarbons to) the molecule at the cysteine residue. This farnesylation of prelamin A helps facilitate its targeting to the inner nuclear membrane. Next, the CaaX portion is cleaved by the ZMPSTE24 enzyme and the cysteine residue leftover is then methylated by ICMT. To complete the posttranscriptional modification, the ZMPSTE24 then cleaves the final 15 amino acids at the endoproteolytic cleavage site. [3]

The mutation responsible for the HGPS phenotype is found in codon 608 of exon 11 of the LMNA gene. A c to t single base substitution causes a silent mutation in the
amino acid sequence, where the Glycine residue remains unchanged. However, the base transition creates a premature splice site that completely erases the final 50 amino acids of the eleventh exon. [2] Since the prelamin A still contains its C-terminus from exon 12, it will still be farnesylated at the CaaX motif. As a consequence of the abnormal splicing, the endoproteolytic cleavage site is absent, resulting in the persistence of the final 15 amino acids and the farnesylated cysteine. [1] This permanently farnesylated mutant protein, termed “progerin”, disturbs the nuclear mesh formed by lamins A and C. It is targeted to the nuclear rim and interferes with the lamina integrity and causes misshapen cell nuclei. [4] This is a perfect example of a dominant negative pattern of inheritance, since one dysfunctional protein disrupts the aggregation of itself with various other proteins that function as a multi-protein complex. In addition to understanding the genetic basis of HGPS, it is also extremely important to apply this knowledge in a clinical setting.

Knowing the biochemistry and molecular biology regarding HGPS enables laboratories and clinics to perform genetic tests on potentially affected patients. Classic HGPS is defined by a completely penetrant de novo dominant mutation involving G608G, as mentioned above. However, in roughly 10 percent of cases, the proband inherits the mutation from one parent exhibiting germline mosaicism. Given this possibility, there is potential for familial recurrence; however, the risk is fairly low, to the order of 1 in 500 siblings. If the parental germline mutation is known, prenatal testing is an option, via amniocentesis or chorionic villus sampling. To perform the test, the DNA is extracted from the fetal cells, and analyzed using the polymerase chain reaction and hybridization with an ASO probe. As with any ASO analysis, the disease-causing allele must be known. The location of tests is limited to a few laboratories around the country, notably including, Baylor College of Medicine and the University of Chicago. Unfortunately, most cases of Progeria go undetected prenatally due to the fact that most are caused by a de novo mutation. Other methods of genetic analysis are available, however they are used as confirmatory tests, not for prenatal diagnosis. For example, sequence analysis and targeted mutation analysis can both be performed at the University of Chicago, among a few other facilities. [1]

Generally, genetic counseling involves explaining how to treat and maintain the disease, as well as how the disease will affect the patient, their family, and future progeny. Since HGPS is overwhelmingly caused by de novo dominant mutations, families are at a lower risk for affectedness. Furthermore, as a consequence of lack of secondary sexual development from failure to thrive and premature mortality (average life span of thirteen years), the affected proband will not reproduce. Therefore, the family planning aspect of genetic counseling is unnecessary with these patients.

**Clinical Symptoms and Diagnosis**

Although children with Hutchinson-Gilford Progeria Syndrome are normal at birth, symptoms normally appear within the first three years of life. They exhibit the following clinical symptoms: stunted growth and short stature, total alopecia or hair loss, delayed dentition, loss of subcutaneous fat, prominent scalp veins, osteoporosis and bone lesions, joint stiffness, prominent eyes, shuffling gait, and abnormal tightness of skin over the upper thighs and abdomen. Additionally, children will often have a distinct facies including thin lips, protruding ears or lack of ear lobes, pinched nose or beaked nasal tip,
and a thin, high-pitched voice. Besides external appearance, HGPS also causes specific deformities of the skeletal system. These include: delayed closure of the anterior fontanelle, a pear-shaped thorax, short clavicles, undersized jaw or mandibular hypoplasia. Diagnosis of HGPS is based on identification of the common clinical features of the disorder as well as molecular genetic testing for the G608G mutation of exon 11, of the LMNA gene. There are two specific testing methods that can be used to identify this specific de novo mutation, gene sequencing or allele-specific mutation analysis. In gene sequencing, a specific segment of DNA is analyzed to determine its nucleotide sequence. Then this sequence can be compared to the known sequence of the normal gene and the known sequence of the mutated gene to determine whether or not that individual has HGPS. Allele-specific mutation analysis or targeted mutation analysis is used to test for one or more specific mutations. Although both of these genetic testing methods have a 100% detection rate for the G608G mutation, gene sequencing is more readily available and is usually the first test done in order to make an accurate clinical diagnosis. It is available at eight laboratories worldwide, while targeted mutation analysis is only done at one of these laboratories. [1]

Unfortunately, the prognosis for children with Hutchinson-Gilford Progeria is poor. They will eventually develop severe atherosclerosis and failure to thrive occurs as a result of heart attack or stroke between the ages of six and twenty, with thirteen years of age being the average age of death. There is no preventative treatment or medications that can slow the progression of HGPS and alter its course. However, if certain complications of the disease arise, there are ways in which to manage these individual symptoms. If abnormalities arise with the lipid profile which measures the amount of total cholesterol, triglycerides, LDL and HDL in the blood, a health diet, physical activity and medication is prescribed. If there is crowding within the mouth due to delayed loss of primary teeth, dental extractions and procedures may be needed. If angina or chest pain develops, medication containing nitroglycerin is often affective. These children are strongly encouraged to engage in physical activity and/or physical therapy with stretching and strengthening exercises to ease joint stiffness and cardiac stress. They are also susceptible to fractures and hip dislocations as a result of coxa valga malformation when the shaft of the femur is bent outward in respect to the neck of the femur, causing bowleggedness. These are treated with body bracing as to avoid surgical procedures. The progression of HGPS in children should be closely monitored via annual lipid profiling, dental examinations, annual electrocardiograms and echocardiograms, and hip x-rays. [1]

It is essential that families and children with this disorder understand that the disease will cause the child to die but until that time, they capable of doing the same activities as other children. Until cardiac complications take over, they can live seemingly normal lives despite their appearance.

Current Research on Treatment for HGPS

Although there is still no concrete method for treating children with Hutchinson-Gilford Progeria Syndrome, there is ongoing research to find possible treatments whereby the progression of the disease may be slowed or altered. In vitro observations have shown that when the farnesylation of prelamin A in cells with the HGPS mutation is blocked by a farnesyltransferase inhibitor (FTI), there is a decrease in the amount of cells with deformed nuclei. A recent study attempted to expand on this hypothesis, by treating
Zmpste24-deficient mice with a farnesyltransferase inhibitor, ABT-100. Mice with this deficiency exhibit the same symptoms as mice with the HGPS mutation such as osteoporosis, stunted growth and short lifespan. Zmpste24-deficient mice that were treated with FTI showed an improvement in survival, increased strength and a decrease in the number of rib fractures. Thus, FTI’s reduce the appearance of Progeria phenotypes in a mouse model, though the disease symptoms were not completely eradicated. Further studies on the benefits of farnesyltransferase inhibitors in children with HGPS need to be conducted. This may prove to be a viable treatment to slow the disease progression. However, early studies on FTI treatment have shown that it is only tolerated for the short-term and thus a long-term solution must be developed. [4]

References: