National Human Genome Research Institute
Hutchinson-Gilford Progeria Syndrome

The gene responsible for the rare and deadly accelerated aging syndrome known as progeria is called LMNA, which is translated into a mutant form of a protein called progerin. The research aims to understand the specific dysfunctions of mutated progerin in the cell by observing cell division, creating a mouse model, testing inhibitors, and starting the first ever human clinical trial. Understanding the variations in the gene and protein product can potentially help treat children with progeria, as well as shed light on the normal aging process.

Lead Agency:

National Human Genome Research Institute (NHGRI)/

National Institutes of Health (NIH)

Agency Mission:

The National Human Genome Research Institute (NHGRI) led the National Institutes of Health's (NIH) contribution to the International Human Genome Project, which had as its primary goal the sequencing of the human genome. This project was successfully completed in April 2003. Now, the NHGRI's mission has expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease.

To that end, NHGRI supports the development of resources and technology that will accelerate genome research and its application to human health. A critical part of the NHGRI mission continues to be the study of the ethical, legal, and social implications (ELSI) of genome research. NHGRI also supports the training of investigators and the dissemination of genome information to the public and to health professionals.

Principal Investigator:

Francis S. Collins, MD, PhD
Director, NHGRI
Building 31, Room 4B09
31 Center Dr, MSC 2152
Bethesda, MD 20892-2152

General Description:

Hutchinson-Gilford progeria syndrome (HGPS) is the most dramatic human syndrome of premature aging. Children with this rare condition are normal at birth, but by age 2 they have stopped growing, lost their hair, and shown skin changes and loss of subcutaneous tissue that resemble the ravages of old age. They rarely live past adolescence, dying almost always of advanced cardiovascular disease (heart attack and stroke). The classic syndrome has never been observed to recur in families. The

laboratory conducting this research discovered that nearly all cases of HGPS harbor a de novo point mutation in codon 608 of the LMNA gene. This mutation causes disease by creating an abnormal splice donor, generating a mRNA with an internal deletion of 150 nt. This is translated into a mutant form of the lamin A protein (referred to now as progerin) that lacks 50 amino acids near the C-terminus. This research has shown that progerin acts as a dominant negative to disrupt the structure of the nuclear membrane scaffold. Recent data has also demonstrated that progerin interferes with proper chromosome segregation during mitosis. A mouse model for HGPS has been developed. Animals carrying a human BAC transgene bearing the codon 608 mutation show progressive loss of smooth muscle cells in the media of large vessels, with replacement by proteoglycan. Thus, the mouse model nicely replicates the cardiovascular phenotype of HGPS.

This project has also explored the possibility that farnesyl transferase inhibitors (FTIs) might be beneficial in HGPS, since lamin A is a farnesylated protein. Treatment of progeria fibroblasts growing in cell culture demonstrates that FTIs are capable of reversing the dramatic nuclear blebbing that is the hallmark of the disease. Based on this data, the research team is conducting a trial of FTIs in the progeria mouse model. A clinical trial of FTIs in children with the disease is planned to be initiated shortly.

Finally, it is hypothesized that other structural or regulatory variants in the LMNA gene might actually be protective against the normal aging process. Accordingly, the lab is also comparing haplotypes in well-matched cohorts of controls and individuals who have achieved exceptional longevity.

Excellence: What makes this project exceptional?

The research team has uncovered remarkable findings about the syndrome as well as its basic biological malfunctions. In addition to discovering the gene responsible and its regulatory pathway inside the cell, the team has discovered that drugs known as farnesyltransferase inhibitors (FTIs), which are currently being tested in people with myeloid leukemia, neurofibromatosis and other conditions, might also provide a potential therapy for children suffering from Hutchinson-Gilford Progeria Syndrome.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Progeria studies are crucial to understand the normal aging process. Understanding the biology of progeria and the mutated form of the LMNA protein also helps researchers understand the normal process that happens in the rest of us.

Effectiveness: What is the impact and/or application of this research to older persons?

If the mutated progerin proteins are able to be slowed down by drugs, the research may provide potential ways to extend longevity and health in the normal population as well.

Innovativeness: Why is this research exciting or newsworthy?

Not only does this research hold promise for children and families affected by progeria by initiating the first ever clinical trial, it also sheds light on the biology of aging and common elderly conditions such as atherosclerotic disease.