We are living in a time that will probably be remembered as a golden age of discovery in human genetics. Most of the recent excitement has focused on the identification of genes that contribute to the risk of common diseases, so it is easy to forget how much can be learned from the study of rare “single-gene” disorders. Although barely noticed by most physicians, these rare disorders can impose an enormous burden on affected patients and their families. Characterization of the gene associated with a disorder provides the key to understanding the relevant pathophysiology, and this understanding may lead to treatments that can ease the condition’s burden. Moreover, insights into the biologic mechanisms of rare disorders may apply to more common disorders as well, with potential benefits for a much larger population.

In this issue of the Journal, the article by Merideth et al. on Hutchinson–Gilford progeria syndrome (pages 592–604) illustrates this concept. This syndrome is among the rarest of conditions, yet it may teach us about mechanisms of one of the most common conditions — old age. In spite of its rarity, most physicians probably have at least a passing familiarity with the Hutchinson–Gilford phenotype, perhaps because it is so striking and heart-wrenching to see young children with the wasted bodies and wizened faces of the elderly. Affected children have a failure to thrive in the early months of life and remain small, with minimal body fat. Thin, sclerotic skin, alopecia, osteoporosis, and progressive cardiac dysfunction develop with age, and most affected children die from myocardial infarction by the early teens.

Identification of the gene responsible for Hutchinson–Gilford progeria syndrome provided an explanation for the rarity of this condition. The gene, LMNA, encodes lamin A, a component of the network of proteins composing the nuclear lamina inside the nuclear membrane.1 Approximately 90% of patients with the syndrome have an identical mutation in one allele of the gene, consisting of a C-to-T substitution at nucleotide 1824 (1824 C→T). The disorder is rare because affected people die before reproductive age, so every case represents a new mutation, and the mutation needs to be precisely targeted to produce the phenotype. Other LMNA mutations are associated with a diverse array of phenotypes, including Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, dilated cardiomyopathy, Charcot–Marie–Tooth disease, familial lipodystrophy, mandibuloacral dysplasia, restrictive dermopathy, and generalized lipodystrophy. Such phenotypic heterogeneity is increasingly being recognized, as the consequences of different mutations in a given single gene are studied. A specific phenotype may initially draw attention to a gene, but it may be the tip of the phenotypic iceberg. Annotation of the phenotypic effects of specific mutations in rare disorders provides a powerful approach to elucidating the function of complex biologic systems.

The LMNA mutation at position 1824 does not change the amino acid of the corresponding codon in the messenger RNA (mRNA). Rather, it causes aberrant mRNA splicing by activating a cryptic splice donor in exon 11, resulting in a protein designated “progerin,” with an internal deletion of 50 amino acids as compared with normal lamin A (see Panel A of diagram).

Lamin A is processed post-translationally through a series of steps (see Panel B of diagram). First, a farnesyl group is attached to a cysteine residue that lies four amino acids away from the C-terminal; this is accomplished by the enzyme farnesyltransferase, and it results in the binding of the nascent protein to the membrane of the endoplasmic reticulum. The final three amino acids are then cleaved by the enzyme ZMPSTE24, and the terminal cysteine is carboxymethylated by a methyltransferase. ZMPSTE24 then makes an additional cut 14 amino acids upstream.
Effects of the LMNA Mutation in the Hutchinson–Gilford Progeria Syndrome.

The LMNA gene includes 12 exons (Panel A). Normal splicing results in lamin A. The 1824 C→T mutation in most patients with Hutchinson–Gilford progeria syndrome activates a cryptic splice donor, causing an abnormal splice that deletes 150 bases from the messenger RNA and therefore 50 amino acids from the C-terminal globular head of the lamin A protein. The abnormal lamin A is called progerin. Lamin A processing (Panel B) begins with the binding of a farnesyl group to a cysteine residue four bases from the end of the protein. Farnesyl transferase recognizes CAAX: the motif cysteine (C), two aliphatic amino acids (AA), and any amino acid (X). The farnesyl group attaches the nascent lamin A to the membrane of the endoplasmic reticulum. The enzyme ZMPSTE24 cleaves the terminal three amino acids, after which the farnesylated cysteine is carboxymethylated (OCH₃). ZMPSTE24 then recognizes a sequence in the globular head, cleaving there and releasing mature lamin A. If the enzyme recognition site is deleted because of the abnormal splice, the abnormal lamin A (progerin) remains farnesylated and bound to the membrane.

of the farnesylated cysteine, releasing the protein from the endoplasmic reticulum into the cytosol and freeing it to be imported into the nucleus. The aberrant splice caused by the 1824 C→T mutation deletes the region targeted by ZMPSTE24, causing the progerin to remain farnesylated and membrane-bound. It does find its way into the nucleus by diffusion through the endoplasmic reticulum, which is continuous with the nuclear membrane, but its continued binding to the nuclear membrane disrupts the nuclear lamina. The phenotypic consequence at the cellular level is blebbing of the nuclear membrane and abnormal binding of chromatin to the nuclear envelope.

How these events cause the clinical phenotype of Hutchinson–Gilford progeria syndrome is not understood. The distorted nuclear membrane may be more susceptible than normal mem-
brane to mechanical damage, leading to increased cell death. Disruption of chromatin or protein binding to the nuclear lamina may lead to dysregulation of gene expression. The nuclear lamina also plays a role in cell replication and DNA repair. Fibroblasts from patients with the syndrome show evidence of unrepaired DNA damage. Furthermore, rendering mice homozygous for Zmpste24 mutations also leads to the continued binding of lamin A to the membrane; fibroblasts from these mice show increased susceptibility to DNA damage.  

Hutchinson–Gilford progeria syndrome is not the only genetic disorder with a phenotype that involves premature aging. Other “progeroid syndromes,” such as Werner’s syndrome and Cockayne’s syndrome, are associated with mutations in genes with products that are involved in DNA repair. Werner’s syndrome shares many phenotypic features with Hutchinson–Gilford progeria syndrome, although the age at onset tends to be later. Werner’s syndrome is usually inherited as an autosomal recessive trait associated with a mutation in the WRN gene, which encodes a DNA helicase involved in DNA repair. Some patients with atypical Werner’s syndrome showing dominant inheritance, however, have LMNA mutations.  

Whatever the pathophysiologic process, knowledge of the molecular defect in Hutchinson–Gilford progeria syndrome has suggested possible therapeutic approaches. It appears that progerin, which is persistently bound by farnesylation to the nuclear membrane, is toxic. It has been hypothesized that interference with farnesylation might reduce this toxicity; this might be accomplished by interfering with production of the farnesy group or by blocking the farnesylation reaction. The farnesyl group is synthesized through the cholesterol biosynthetic pathway, and drugs such as statins and bisphosphonates are known to reduce its production. Farnesyl transferase inhibitors have been developed because of the role of farnesylation in the function of ras, an oncprotein involved in many forms of cancer. Such agents have been shown to diminish the nuclear blebbing of cells from patients with Hutchinson–Gilford progeria syndrome in vitro and to ameliorate a Hutchinson–Gilford–like phenotype in a mouse model with a heterozygous Lmna mutation. Although there are side effects, children with cancer who have been treated with farnesyl transferase inhibitors have an acceptable side-effect profile. Other therapeutic approaches to Hutchinson–Gilford progeria syndrome that have been considered are the use of small RNA molecules to inhibit lamin A production (RNA interference) and oligonucleotides that bind to the mutant splice donor to inhibit the abnormal splicing event.

Some of these therapies involve drugs that are already available and known to be safe in children. Conducting a clinical trial in children with the syndrome, however, requires precise documentation of the phenotype and careful selection of outcome measures. Merideth et al. provide the most complete and quantitative analysis of the Hutchinson–Gilford phenotype to date, including measurable variables and natural history data; this analysis will pro-
vide the necessary groundwork for an open-label clinical trial.

Will the lessons learned from the study of this syndrome apply to the “normal” aging process? The aberrant splice in lamin A mRNA does occur to some extent in normal cells, and Hutchinson–Gilford–like nuclear changes have been seen in cultured fibroblasts from older persons. Whether these changes contribute to normal aging is unknown, but it is striking that treatment of fibroblasts from older persons with an oligonucleotide that interferes with the aberrant splice reversed the effect.

At the least, lamin A provides a handle for the study of cellular processes that can contribute to the “phenotype” of aging, a point that would probably not have been appreciated without knowledge of its role in the Hutchinson–Gilford progeria syndrome.

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