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Mutation provides new insight into the molecular mechanisms of aging

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A new study identifies the mutation that underlies a rare, inherited accelerated-aging disease and provides key insight into normal human aging. The research, published by Cell Press online May 5 in the *American Journal of Human Genetics,* highlights the importance of a cellular structure called the "nuclear envelope" in the process of aging.

"Aging is a very complex process which affects most biological functions of an organism but whose molecular basis remains largely unknown," explains Dr. Carlos López-Otín from the University of Oviedo in Spain. "Over the last few years, our knowledge of the molecular mechanisms underlying human aging has benefited from studies of premature-aging syndromes, such as Hutchinson-Gilford Progeria syndrome, that cause the early development of characteristics normally associated with advanced age."

Previous work has implicated defects in DNA repair systems in human progeria, and more recent studies have also implicated alterations in the nuclear envelope. The nuclear envelope is a structure that surrounds the nucleus of a cell. The nucleus houses the cell's genome, and the nuclear envelope interacts with DNA and regulates the exchange of materials, such as transcription factors that control gene expression, into and out of the nucleus. Mutations in genes for proteins called "lamins" that form major parts of the nuclear envelope have been linked with progeroid syndromes by this group and others. However, other patients do not exhibit mutations in known candidate genes, suggesting the existence of additional genes implicated in premature aging.

To gain new insight into the molecular mechanisms implicated in accelerated aging, Dr. López-Otín and colleagues sequenced the coding regions of all genes in two unrelated families with a novel progeroid syndrome. This study revealed a mutation in a gene called barrier-to-autointegration factor 1 (BANF1). Both patients had a dramatic reduction in the protein produced by this gene, and their cells exhibited substantial abnormalities in the nuclear envelope. These nuclear defects could be rescued by expression of normal BANF1.

"The finding of mutations in BANF1 associated with a progeroid syndrome may allow the development of therapeutic approaches for patients with this condition, as previously done for other progeroid syndromes," says Dr. López-Otín. "Furthermore, this study underscores the importance of the nuclear lamina for human aging and demonstrates the utility of the new methods of genome sequencing to identify the genetic cause of rare and devastating diseases which have traditionally received limited attention."

Provided by Cell Press