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Promising research on the susceptibility to and drug targets for Parkinson's disease

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Better understanding of Parkinson's disease onset during aging is important for improving diagnostics and developing strategies for therapeutic intervention. Scientists from the University Medical Center in Groningen have now identified genes and processes that may underlie what makes some people more susceptible to this disease. Their findings are described in an article published March 21 in the open-access journal *PLoS Genetics*.

On average, the population of the western world is living longer, resulting in an increased number of people with age-related neurological conditions, including Alzheimer's and Parkinson's disease. A cure for these diseases remains elusive because their molecular cause is only partially understood. It has been noted, however, that accumulations of folded proteins are commonly found within the brain cells of those who suffer from these diseases. For this reason "protein misfolding" seems to form the basis of these diseases.

To gain insight into the cellular processes that play a role in protein misfolding, the research group, led by Ellen Nollen, looked for genes in the round worm Caenorhabditis elegans that, if switched off, cause the number of inclusions to increase. During the course of their research, the scientists individually switched off 17,000 of the 19,000 genes and studied the effect on protein formation.

The study findings indicate that the gene sir-2.1 has a considerable effect on protein formation. In humans, this gene, called SIRT1, is

evolutionarily conserved and is involved in the aging of yeast, flies, and worms and probably also in mammals. It lengthens the lifespan of worms by the activation of various routes through which signals are transmitted (stress response and insulin signal transduction). These findings suggest that sir 2.1 may represent a possible mechanistic relationship between aging and Parkinson's disease.

The accumulation of proteins has been shown to be strongly age-dependent and to occur in clearly distinguishable phases. From RNA-interference screening, it appears that the manner in which proteins accumulate in the roundworm model can be clearly differentiated from that of other diseases in which the aggregation of proteins occurs. Moreover, it shows a clear link with the aging process, in which the membranes of the endoplasmatic reticulum/Golgi system of the cell probably play a role. This study points the way towards further clarification of the pathological mechanisms of, and the genetic susceptibility to, Parkinson's disease and other conditions in which the disease-specific protein alpha-synuclein plays a role.

Citation: van Ham TJ, Thijssen KL, Breitling R, Hofstra RMW, Plasterk RHA, et al. (2008) C. elegans Model Identifies Genetic Modifiers of a-Synuclein Inclusion Formation During Aging. PLoS Genet 4(3): e1000027. doi:10.1371/journal.pgen.1000027

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