Bart Deplancke examines the genes of hundreds of fruit flies in order to unravel the mystery of cellular aging.

Systems biology of aging (AgingX)

Our fate lies in our genes

Getting old is easy, but doing so healthily is not. This is why researchers at the EPF Lausanne are investigating the genetic basis of the body's decline in old age. Their findings could help us live healthier for longer.

It seems that the members of some families live much longer than others, with some, for example, living to a ripe old age of over 90 despite smoking heavily their whole lives. Researchers now know that our genes are largely responsible for such long lifespans, although exactly which genes play a role is as yet unknown.

Bart Deplancke, bioengineer and head of the Laboratory for Systems Biology and Genetics at the EPF Lausanne, wants to change this. He is the project leader of the AgingX project, which takes a closer look at the hereditary causes of aging.

The project focuses largely on establishing the genetic factors contributing to a long healthspan; that is, the part of our lives in which we are relatively fit and healthy. Sadly, many people simply become sicker as they grow older. "We want to find out in what ways some people are genetically predisposed to healthy old age and how their genetic make-up slows the aging process", explains Deplancke.

Eliminating environmental factors

These questions are extremely difficult to answer. There are around 25,000 genes in the human genome. Researchers have already managed to link a few hundred of these to the aging process, although exactly which combinations help us grow old in good health is still unknown. To make things even more complicated, environmental factors such as diet, exercise or smoking habits can influence whether or not our genes can exploit their full potential.

With AgingX, Deplancke and his collaborators want to remove such environmental factors from the equation to gain an unclouded view of the complex interplay of genes. To tackle this, four research groups work together to combine their expertise. They work with mice and fruit flies, all of which live in a standardized environment. Every animal receives the same food and lives under the same light and temperature conditions.

Inbreeding sheds light on aging process

Even the animals' genomes need to be standardized. This is why Deplancke's colleague at EPFL, Johan Auwerx, works with 60 inbred mouse strains. Each mouse from any one of these strains can be traced back to one female and one male mouse, which also came from inbred strains.

Normal mice possess two sets of genes, one from the mother and one from the father. This is like an insurance policy. If one gene is missing or faulty, its partner can take over the job. These conditions are however not very practical for statistical analysis, as it is impossible to tell which of the two genes is active in any one mouse. With an inbred mouse strain, this is no longer a problem, since both sets of genes are identical.

The researchers are now observing the life cycles of these mice. They are particularly interested in their fitness and time of death. The initial results are striking. Despite the fact that these 60 mice strains all belong to the same "family", the lifespan varies hugely from mouse to mouse.

"Mice typically live for about two or three years", explains the project leader, "but the Auwerx Lab has identified some mice strains which have already passed the three-year mark and are still going strong." Other strains, in contrast, died of old age after just a year and a half.

This means that the oldest mouse lived at least twice as long as the mouse that died youngest due to its particular combination of genes. "This shows us that even just the distribution of maternal and paternal genes has a huge impact on the lifespan", concludes Deplancke. The analysis of the results will later tell us which combinations of genes contribute to a long, healthy life.

In the next step, the researchers aim to investigate the healthspan of the mice in the same way. "This, however, is more difficult to measure", says Deplancke. To analyze this, the mice are for example put in an exercise wheel at regular intervals, where they undergo a sort of fitness test.

The cell's powerhouse

Another important topic for AgingX is mitochondria. These are tiny powerhouses that supply our cells with energy. They are the only organelles within cells that possess their own DNA. Deplancke suspects that even here, there could be genes or combinations thereof, which influence our health- and lifespans. "The mitochondrial genome has often been neglected in research until now. That's why we're taking a closer look", says Deplancke.

Mitochondria convert sugars and fats into chemical energy, which drives every process in a living organism, from muscle contraction to the transmission of nerve impulses in the brain. We know that the cell's energy supply becomes less reliable with age, leading to ailments such as obesity, diabetes, cardiovascular disease and fatty liver.

To find out which mitochondrial genes contribute to particularly rapid aging, Deplancke and his team work with 140 strains of fruit flies. These flies must also undergo regular fitness tests. The flies are placed in a glass tube with a beam of light in the center. The fitter the fly, the more often it crosses this light barrier. A computer registers each occurrence, establishing how active each fly is. The fruit flies' genes being known, it is possible to then link them to the fitness data.

The statistical analyses from both experiments are currently underway. Ideally, Deplancke and his colleagues will be left with a list of genes and gene combinations known to contribute to a long, healthy life. "We will then compare these results with the human genome", says Deplancke. Flies share around 60 percent of their genes with humans, and mice 80 percent, meaning that many of these results will be relevant for us, too.

Living healthier, longer

This knowledge will one day help us to stay fit as long as we can. "In the future it will be completely normal to have a genetic test done at the age of 20 or so, to find out one's life expectancy", predicts Deplancke. But that's not all. A genetic test may also be able to show which bodily systems will be the first to degenerate. "If we had this information, we would be able to take preventative measures in our youth", enthuses Deplancke. For example, if the test shows that muscular atrophy is due to set in at the age of 60, the affected person could start attending regular muscle-building training at the age of 50, or taking medication which hinders progress of the disease. "We will live longer, healthier and happier lives", says Deplancke.

AgingX at a glance

Principal investigator: Prof. Bart Deplancke

Research groups:

- Prof. Bart Deplancke, Institute of Bioengineering, EPF Lausanne – Systems genetics
- Prof. Johan Auwerx, Institute of Bioengineering, EPF Lausanne – Systems physiology and genetics
- Dr. Zoltan Kutalik, Department of Medical Genetics, University of Lausanne – Medical genetics and statistics
- Prof. Marc Robinson-Rechavi, Department of Ecology and Evolution, University of Lausanne – Evolutionary and computational biology

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AgingX
Systems Genetics Approach to the Biology of Aging