Polyglutamine repeats play key role in functional development of cells

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Scientists at VIB and KU Leuven have revealed that variable polyglutamine repeats in the DNA tune the function of the protein in which they reside. To date, these repeats were known only to cause severe neurodegenerative diseases such as Huntington's. These findings now show that polyglutamine repeats may be more than just harmful elements. The study was published in the leading molecular biology journal *Molecular Cell* and opens the door to further studies exploring new therapies for human polyglutamine repeat diseases. Moreover, this study lays the foundation for future research into the role of repeats in the emergence and evolution of novel functions and life forms.

Excessive numbers of glutamine-rich repeats in various human proteins are known to result in severe neurodegenerative disorders such as Huntington's disease. Little is known, however, about the physiological role of these repeats and the consequences of more moderate repeat expansion.

Rita Gemayel (VIB/KU Leuven): "We found that the polyglutamine repeats act like the dial on a tuner. The length of the repeat modulates the transcriptional response of genes in the cell. More specifically, using a polyglutamine-containing protein called Ssn6 as a model, we showed that the repeat length modulates the solubility of Ssn6 and its interaction with other proteins. When the dial is turned too far and repeats are abnormally expanded - similarly to what happens in polyglutamine diseases - the function of the Ssn6 protein deteriorates. It then no longer interacts properly with its normal partners and aggregates with other

proteins, potentially leading to neurodegenerative diseases."

Not solely harmful after all

Rita Gemayel (VIB/KU Leuven) and a research team led by Kevin Verstrepen (VIB/KU Leuven) noticed that genes displaying regulatory functions are particularly rich in polyglutamine repeats. This observation applied not only to simple organisms such as yeast, but also to more complex organisms such as humans. Their subsequent study revealed how expanded numbers of polyglutamine repeats may be more than just potentially harmful elements in genomes. Instead, they may play an important role in tuning the development of healthy cells and organisms.

Using a strain of brewer's yeast, the team created a range of cells that were identical except for the number of polyglutamine repeats in Ssn6, a protein that regulates the function of certain genes. Analysis showed that incremental changes in the number of repeats caused non-harmful variations in the expression of the genes regulated by Ssn6. In other words, repeat number variations resemble tuning knobs that create dynamic and gradual changes in the physiology of the cell.

More information: "Variable Glutamine-Rich Repeats Modulate Transcription Factor Activity." *Molecular Cell*, Available online 6 August 2015, ISSN 1097-2765, dx.doi.org/10.1016/j.molcel.2015.07.003

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