A nervous switch

In 1863 a Heidelberg doctor described a devastating neurodegenerative condition that causes children to forget how to walk and talk before their teens. The symptoms begin with muscle weakness, poor balance and a slurring of speech, and develop into a gradual breakdown in all motor control. Mysteriously, physicians sometimes noticed similar, although milder, symptoms in the parents of afflicted children, and even milder effects in the grandparents, suggesting that the disease might result from a genetic defect that grows more and more severe each generation. Only in the 1990s did geneticists discover long tracks of the amino acid glutamine within certain proteins of children suffering from these strange neurological symptoms. Substantially lengthening these glutamine tracks caused the proteins to clump together in the nuclei of cells – usually nerve cells – leading to the cell's demise. At least nine inherited diseases, which can affect both adults and children and include Huntington's disease, are known to result from these repeat mutations.

But these glutamine repeats, it seems, are not solely to blame for the deteriorating nerve control. For clues to other contributing factors to the development of these diseases, scientists are trying to identify the roles of the affected proteins.

One such protein, which causes a rare but devastating neurological condition known as spinocerebellar ataxia type 1, is the focus of chemist Annalisa Pastore, a former EMBL group leader who now works at the National Institute for Medical Research in London. Annalisa hopes to gain clues about the function of this protein – called Ataxin-1 – by investigating its structural form to predict with which molecules it interacts. However, Ataxin-1, unlike most proteins, does not fold into three-dimensional shapes, but instead remains floppy and mostly unfolded. Thus, the structural models most researchers usually use to predict protein–protein interactions were of no use for this protein.

Toby Gibson

So Annalisa teamed up with computational biologist Toby Gibson from EMBL Heidelberg, who has developed a computer program to search for interaction sites on the non-folded regions of proteins. The researchers applied this bioinformatic resource, called the Eukaryotic Linear Motif Resource, to compare the amino-acid sequence of Ataxin-1 across many species, ranging from mosquitoes to zebrafish to humans. In this way, they sought to predict which short regions, or motifs, of Ataxin-1's amino-acid sequence might interact with other proteins.

"Annalisa and I were sitting together when my database threw up a promising candidate motif that suggested that Ataxin-1 might interact with a protein, called U2AF65, that regulates alternative splicing – a means by which a single gene can produce many variants," says Toby. "But what got Annalisa even more excited was that this motif overlapped with an existing motif that was already known to interact with two other proteins," says Toby.

In the lab, Annalisa and her group confirmed Ataxin-1's role in alternative splicing – an important find for scientists examining proteins involved in these neurological diseases for clues about why they are the targets of glutamine repeats. Annalisa also verified that she and Toby had spotted in the database a three-way molecular switch, which involves three proteins binding at one interaction site. "What is key in this case is that Ataxin-1 can only bind one of its interacting proteins at a time," Toby explains.

Toby's group is keen to find more motifs that could be important for the development of many other diseases. "We suspect that there are over a million of these regulatory motifs in human proteins, and you could say that it is my team's holy grail to learn how to find them all!" Toby says.

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de Chiara C, Menon R, Strom M, Gibson T, Pastore A (2009) Phosphorylation of S776 and 14-3-3 Binding Modulate Ataxin-1 Interaction with Splicing Factors. *PLoS ONE*: **4**