

So the little pink protein is ubiquitin and our yellow protein here is ataxin-1. For ubiquitin to be carried to proteins it needs a carrier, it's called the ubiquitin carrier enzyme. Once our ataxin has done its function and it's ready to be degraded, another enzyme will come, a ligase, ubiquitin ligase will come and attach to it. The ligase will interact with the carrier and take the ubiquitin from the carrier back to our protein. And now it can put more and more ubiquitin molecules. A protein will have to have multiple ubiquitin molecules to be degraded, and now once it's flagged the proteasome recognizes it's ready for degradation. The proteasome has a cap, the cap opens the protein unwinds and enters the business ends of this proteasome, the catalytic core that chops this protein up into little pieces, and this protein will be degraded, and the peptides and amino acids recycled. So this is really what happens for many, many, many cellular proteins. It's a very important process, and these are the players. Now imagine mutant ataxin1 it has a different shape, and it's getting ubiquitinated, gets to the proteasome, but its shape is so unusual, it's just not as flexible perhaps, we think at least that may be what is happening, but it just can't quite unwind and get through that proteasome. It's stuck. And that's what we think is happening at least based on some data looking at tissues and cells we had some evidence and support of this.