example, several rare genetic mutations in SNCA—the gene cod- ing for α-synuclein—are associated with elevated Parkinson’s risk, but the relationship isn’t straightforward. At least in vitro, mutations in α-synuclein that cause Parkinson’s disease do not closely correlate with their propensity for aggregation,” Edwards explains. “There are some that reduce their propensity for aggre-gation, others increase it. So there’s something we’re missing.”

In light of these and other observations, many research- ers working on neurodegenerative disease have come to see protein aggregation as a hypothesis, rather than the primary cause, of neurological damage, says David Sulzer, a neurosci- entist and Parkinson’s expert at Columbia University who has collaborated with Edwards. Still, settling on an alternative explanation for how neurodegenerative diseases arise isn’t easy. Most current hypotheses revolve around inflammation caused by viral infection or defects in cellular waste disposal. “My hypothesis is that there’s a problem in the normal function of α-synuclein degradation, which leads to the [aggregation] but it’s also leading to cellular damage that eventually ends up causing Parkinson’s,” says Sulzer. He adds that similar waste-disposal hypotheses have been proposed to explain some of the pathology of Alzheimer’s.

Other researchers see a different possibility: that problems in neurodegenerative disease start with disruption to the normal functions of the aggregating proteins themselves. Investigating this idea in Parkinson’s, Edwards and his col-lleagues have conducted animal studies that replicate some of the mutations associated with elevated Parkinson’s risk to see how they affect α-synuclein’s activity. One such experiment built on the team’s finding that α-synuclein affects few vesicles fuse with the cell membrane, speeding up the release of their cargo. Using mice and cultured rat neurons, the researchers discovered that SNCA mutations associated with Parkinson’s disease seem to specifically disrupt this function. “This means that some of these mutations might have lower-than-normal neurotransmitter release, something that could ultimately contrib- ute to neuronal death, Edwards speculates. Of course, only a fraction of people who get Parkinson’s have mutated copies of SNCA. But the team’s work hints that genetic or environmental disruptions to a pathway involving α-synuclein may contribute to disease pathologies.

Hassan has been exploring similar ideas as they relate to APP and Alzheimer’s. For example, he and others have noted that certain rare mutations in APP that are associated with some early-onset cases of the disease may alter APP’s regu-lar activity. Using fruit flies, which have a homologous ver-sion of APP called APPL, Hassan’s lab discovered that deleting the underlying gene or blocking production of the protein was associated with increased neuronal death, particularly in young flies, as well as problems in intracellular trafficking and other important cellular processes.” While losing APP entirely via genetic knockout isn’t the same as having a mutated version of the protein, the findings point to potential neurological consequences of reduced or altered APP func-tion, Hassan argues.

Some groups have also focused on these proteins’ role in mammalian brain development. Humbert, for example, says she’s interested in whether changes in HTT’s activity might set the stage for developmental abnormalities, even if clinical symptoms of Huntington’s disease don’t show up until a person’s 30s or 40s. She points to evidence from her labs suggesting that animals engineered to express lower-than-normal levels of HTT as embryos but normal levels as adults show abnormal brain development as well as later-life neuronal degeneration.

In the last couple of years, her own group has reported that mouse embryos expressing mutated versions of huntingtin show disruptions in cell growth and intracellular dynam-ics in neurons, leading to differences in neuronal prolifera-tion and, ultimately, a difference in cortex structure between mutant mice and controls. A recent study the lab carried out using small sections of neural tissue from human fetuses hinted at a similar pattern in people: compared with controls, carriers of mutant HTT had a differently developed cortex at the end of the first trimester. “These findings may help explain some brain imaging studies that suggest people with Hun-tington’s have altered cortical organization as well as an early-on-ward change, even before the classical cognitive and motor symptoms of the disease emerge,” Humbert speculates. “We are showing that abnormal development may contribute to preclinical symptoms.”

Humbert notes that she and her colleagues have recently started discussing parallels in their research, despite studying different neurodegenerative diseases. Hassan’s group is now working on understanding APP’s role in brain development and how that role may vary across the animal kingdom—early observations with cultured human cells and rodents, for example, hint that the protein may be more important for neurogenesis in people than it is in mice. Animal studies are only so informative about the human brain—more study of cultured human neurons may not capture what really happens during in utero development, several researchers note.

A tangled explanation
For now, the evidence for a causal connection between disrup-tion in normal protein function and the onset of neurogene-ric diseases is still thin, and researchers working in the field are the first to acknowledge the challenge of closing the gap. Animal studies are only so informative about the human brain—particularly when mice and other lab animals don’t develop any-thing like human neurodegenerative disease. Moreover, in vitro studies of cultured human neurons may not capture what really happens during in utero development, several researchers note.