# How proteins assemble may have underappreciated role in disease

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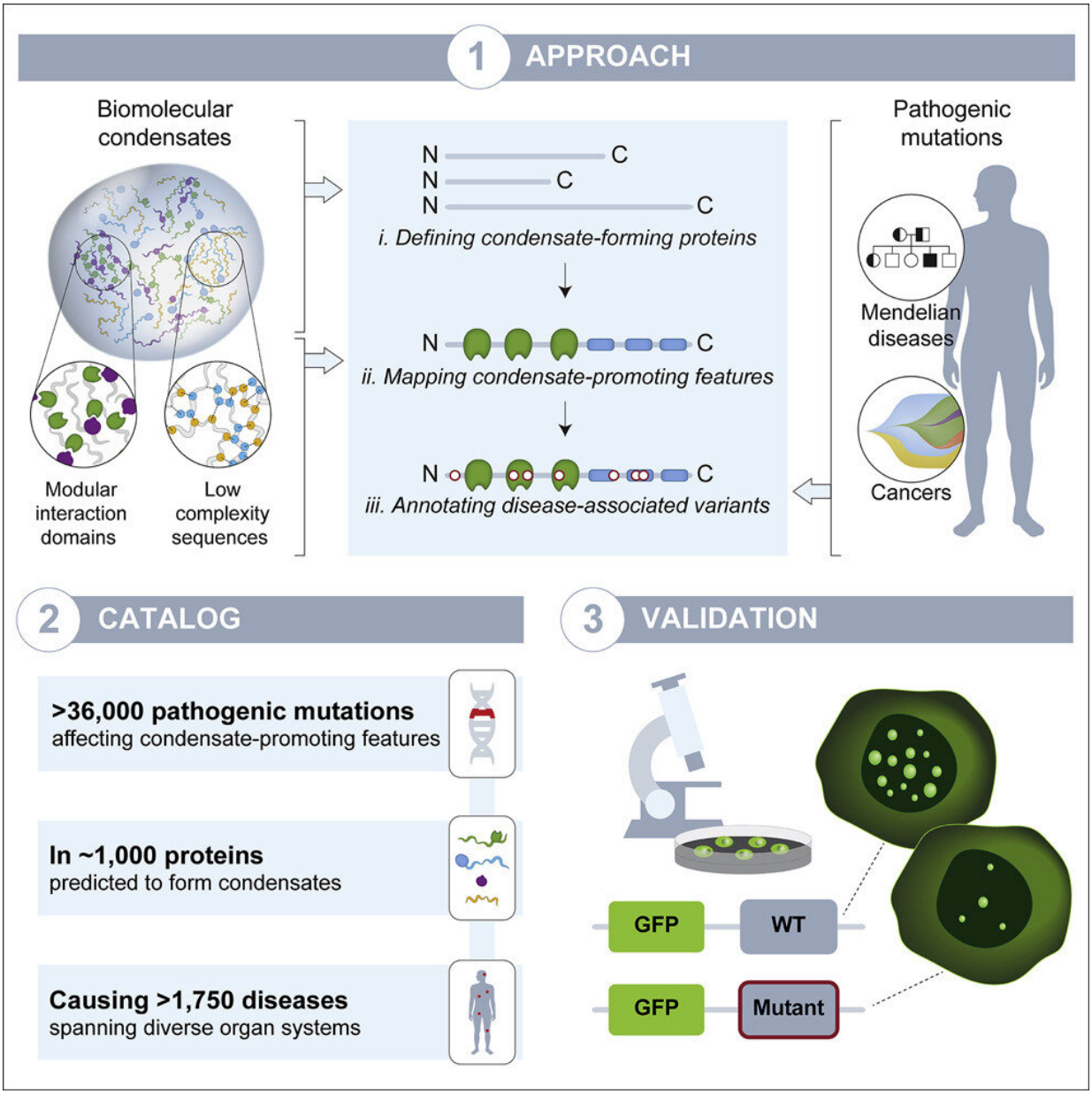

Graphical abstract. Credit: *Developmental Cell* (2022). DOI: 10.1016/j.devcel.2022.06.010

Thanks to advances in genomics in recent decades, researchers now know the genetic mutations responsible for many diseases. However, researchers often still do not know how the mutation leads to the disease—what it changes inside of cells to cause symptoms. Figuring out this missing piece, the disease mechanism, not only advances understanding of the disease but can be essential for developing a treatment or prevention. For example, if researchers know that a mutation leads to the creation of a faulty protein, and that the build-up of this faulty protein causes the disease, then they can design drugs that will lead to the protein's destruction.

Researchers in Whitehead Institute Member Richard Young's lab have been studying a process called biomolecular condensation that helps organize where molecules end up in cells, and they suspected that disruption of this process might be an underappreciated, common mechanism of disease. Condensates are structures that form when many molecules loosely mesh together to create a droplet that separates out from the other contents of the cell, like an oil drop suspended in water. The Young lab's latest research, published in *Developmental Cell* on July 8, suggests that disruption of condensates is indeed pervasive across disease types throughout the body. The paper provides researchers with a catalog of likely instances. They hope that this catalog will be used to further understanding of diseases in which condensates play a role and, ultimately, to develop new therapies for those diseases.

## Growing awareness of condensate biology

Only certain molecules—some proteins and RNAs—form condensates,

because they contain regions that are capable of loosely binding together. Most proteins have regions that bind very strongly only to specific molecules, like a key slotting firmly into a lock. Condensate-forming proteins instead tend to make lots of loose, less specific connections with each other, meshing together in high concentrations until they create a droplet. Cells use condensates to gather molecules where they are needed within the cell—for example, molecules needed to transcribe genes may form condensates near those genes.

Condensate researchers including Young, who is also a professor of biology at the Massachusetts Institute of Technology, have shown in recent years that condensates play roles in many important cellular processes. Condensate disruption has also been shown to occur in a small but growing number of diseases, in particular neurodegenerative disorders. However, when researchers are hunting for disease mechanisms, condensate disruption is not often considered. Given how commonly condensates play a role in healthy biology, Young lab researchers suspected that their disruption might be common in disease. Postdoc in the Young lab and co-first author Salman Banani, who is also a pathologist at the Brigham and Women's Hospital, began suspecting as much during his clinical training, while looking at genetic sequencing data for cancer patients.

"The goal was to assess the clinical relevance of the mutations in the tumors' genomes and how that might impact care for each patient. I noticed that many of the mutations I was examining were suspiciously affecting regions of the protein that I thought might be involved in condensation," Banani says. "That led me to wonder how often human disease mutations affect condensate forming regions, if we had overlooked a potentially widespread cause of human disease, and whether pathologists should consider condensation properties in any of our assessments of mutations."

When Banani joined the Young lab, the potential clinical significance of mutations in condensate-forming proteins was fresh on his mind. Graduate students in the Young lab and co-first authors on the paper Lena Afeyan and Susana Wilson Hawken, who had been studying how drugs interact with condensates, were also eager to tackle the question of how broadly condensates contribute to disease.

## Condensates and disease

The researchers compiled a list of proteins thought to form condensates, and mapped the locations of condensate-forming regions within each protein. They also made a list of genetic mutations known to cause or contribute to a wide variety of diseases, including diseases in which a mutation to a single gene is responsible for the disease and a number of cancers. Next, the researchers mapped each mutation to the part of each protein it affects. From this work, they created a list of disease-causing mutations that occur within the condensate-forming regions of the proteins. They hypothesized that these mutations would be most likely to affect the proteins' ability to form condensates.

The researchers ended up with a catalog of more than 36,000 disease-causing mutations, affecting more than 1,000 proteins, that likely disrupt condensates. The mutations in the catalog contribute to more that 1,700 diseases, including more than 550 cancers, collectively affecting every part of the body. Now, the researchers hope, people studying those diseases can use their catalog as a jumping off point to test if condensate disruption may in fact be a mechanism underlying the disease. This may in turn provide opportunities to develop therapies that target condensates.

"If we now know that a mutation affects a protein that likely resides in a condensate, we can test in cells to see whether and how the mutation affects the condensates and whether this effect is relevant for the

underlying disease," Wilson Hawken says. "Then we could test a panel of drugs to see if we could rescue normal condensate formation and if this would be a good way to treat that particular disease."

The researchers tested a sample of the proteins and mutations from their catalog to verify that the catalog is a good predictor of mutations that disrupt condensates. They selected thirteen proteins that are able to form condensates in mouse embryonic stem cells, and introduced relevant disease-causing mutations to the proteins within those cells. Of the fifteen mutations they introduced, thirteen disrupted condensates; this high rate of disruption suggests that the catalog is a strong predictive tool.

Interestingly, different mutations disrupted condensates in different ways. The most common effect was to reduce the proteins' ability to join condensates. However, one mutation instead increased the proteins' ability to join condensates, and another affected where the condensates ended up in cells—all over the cell instead of contained within the nucleus. Determining the specific way in which a mutation affects condensates will be important for understanding disease mechanisms and developing drugs to reverse the mutation's effects.

"This catalog is a great starting point to ask lots of questions about condensate dysregulation as a disease mechanism, such as how do changes in the properties of condensates affect the cellular processes happening in these condensates? We and others believe condensates could have profound implications for disease and drug development, just as they have had in basic molecular biology, and our hope with this catalog is that we can lower the barrier to entry for many more disease researchers to start studying them," Afeyan says.

The researchers hope that their catalog proves useful in others' research, and they also hope that it raises awareness of the likely pervasiveness of

condensate dysregulation in diseases, even beyond the instances in the catalog.

"There are likely many cases not covered by the catalog, such as when the mutation does not directly affect the condensate-forming protein, but rather affects one of its regulators," Young says. "I think we are just seeing the tip of the iceberg in terms of the prevalence of condensate dysregulation in disease. My vision for the future is that researchers will consider a condensate model among the conventional models when searching for the potential underlying disease mechanism of any mutation."

**More information:** Salman F. Banani et al, Genetic variation associated with condensate dysregulation in disease, *Developmental Cell* (2022). DOI: 10.1016/j.devcel.2022.06.010

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