Model shows how mutation tips biochemistry to cause Alzheimer's

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Your fate can be determined by tiny events. Imagine you live in the city and you walk everywhere to get exercise – you are healthy and not afraid of getting mugged. You almost never eat breakfast so you don't stop at the donut shop on the way to work, until one day the manager replaces the girl at the counter with her pretty red-haired younger sister. This seemingly unimportant change in your world is just enough to overcome your ability to resist high-fat temptation. A million donuts later, your cholesterol level surges and then your heart gives out. Curse you, little red-haired girl!

Like staff change at the donut shop, subtle, seemingly inconsequential differences in human genetic design can lead to some unexpected tipping points in cellular chemistry that can lead to disaster. Cellular processes, like all the routines of life, are unfathomably complex, constantly evolving, and are sometimes dramatically sensitive to the smallest of changes. Consider the case of Alzheimer's disease…

Alzheimer's is a terrifying brain-destroying disease whose causes have proven very difficult to pin down. In recent years, science has been closing in on solving the puzzle, particularly regarding some of the hereditary, "early onset" forms of the illness. Unusual by-products of cell metabolism, clumps of protein aggregates, have been shown to have a toxic effect on brain cells and certain gene mutations have been shown to be associated with increasing production of these by-products, though the evidence for an exact mechanism has remained hidden.

Now, using sophisticated computer simulations, a team of physical chemists have shown precisely how a minor, seemingly inconsequential mutation results in unexpected changes in a very delicate chemical balance, creating build-up of the toxic by-products.

The mutation, the substitution of a single base among the 3 billion found in human DNA, seems to have the greatest effect on a fragment of a specific protein that is abundantly present in living cells. The difference causes a subtle change in the shape of the fragment at a critical point, which can slightly shift the odds towards an inappropriate biochemical reaction that sidetracks the metabolic path. The increase in the reaction simply tips the balance of chemical processes, causing the build-up of a substance that kills brain cells, leading to the early deterioration of mental capacity and, eventually, death.

“It is a really tiny change but it has tremendous consequences,” said Andrij Baumketner, lead author on the study and a faculty member in the department of physics and optical science at the University of North Carolina at Charlotte. The finding, published in the April 7 issue of the Publication of the National Academy of Sciences, was co-authored by Mary Griffin Krone and Joan-Emma Shea, both from the department of chemistry and biochemistry at the University of California at Santa Barbara.

The group studied the effects caused by the Dutch Mutation, a mutation that has been discovered to be associated with a specific, hereditary form of Alzheimer’s disease. The mutation is small, the simple substitution of one DNA base for another, resulting in the change of only one amino acid residue – glutamic acid changing to the very similar glutamine – among hundreds of amino acids that form a protein known as the amyloid precursor protein (APP). The greatest effect of the Dutch-type mutation on APP, whose primary biological function is unknown, seems to be through a fragment known as amyloid-beta peptide that is

created when cells break down the protein. Studies have shown that mutated forms of the fragment have greater tendency to stick to bond together and form protein clumps or aggregates. Some forms of the amyloid-beta clumps have been shown to be toxic to brain cells.

Why the change in one amino acid would cause this peptide to form clumps more readily has, until now, been unclear. Amyloid-beta peptide, unlike most other proteins present in the cell, is largely lacking in specific shape (conformation), the characteristic that usually controls how proteins interact with each other. However the fragment does have two places in its sequence of amino acids – a section known as the "bend" and an area known as the "central hydrophobic cluster" where the polypeptide chain does conform to a more-or-less fixed shape. These areas, in fact, seem to be involved when the fragments bond together into clumps.

The researchers created complex computer models of the two structured areas of the fragment and found that the single amino acid change caused by the mutation had a subtle effect on their properties. In order for fragments to bond together, the structured areas must first undergo a "conformational change" (a change in structural shape) from the conformations they normally have as single, water-soluble amyloid-beta peptides into a "transition state" conformation that leads up to forming clumps. The researchers found that mutation increased the likelihood that the structures would be in a form similar to the transition state before the reaction occurred. When the structured areas were already in the required transition state, bonding was encouraged because less energy was required for the bonding reaction to take place.

"We knew quite a bit about what these peptides are from experimental studies, but we didn't know the microscopic details," noted Baumketner. "An experiment never gives you atomic resolution – you always have to guess what is actually going on with the molecules. But with a computer

simulation you start with atoms and how they interact and you end with atoms, so there is no question with missing any details."

The detail of the simulations showed that, because the mutation made the protein fragments more likely to be in a transition state for bonding, bonds between fragments were more likely to be formed than broken (in the reverse reaction), so clumps of fragments accumulated. The end result of the subtle, mutation-driven change in the protein fragment's shape was the tipping the reaction's balance enough to allow clumps composed of multiple fragments to occur and to build up --with a disastrous effect on brain tissue.

"The barrier between the reactants and the products is the conformational difference between the peptide and its transition state," Baumketner said. "The fewer changes the peptide needs to undergo, the easier it is for it to change. The mutation predisposes the single amyloid-beta peptide to jump onto the barrier that keeps the reaction from happening."

The ultimate problem responsible for Alzheimer's Disease, Baumketner notes, is that the design of the protein affected is so "close to the edge" in the reactions it must undergo that extremely small changes can cause problems, like the formation of toxic by-products.

"It looks like whoever designed the proteins in our bodies only made the beta peptides to be right on the edge of where they have to be for us to be alive," he said facetiously. "You make a small push and you push it over the edge and then there is no return. If you were farther from the edge, that would be fine, and you could tolerate one mutation.

"There is lots of discussion about why this happens – is it the failure of evolution? Maybe evolution never has had a chance to optimize us against this. Humans now live to be much older, but evolution never has

had a chance before to detect and avoid these problems through natural selection. When the lifespan was 35 years, you didn’t have a large problem with Alzheimer’s. Now you do.”

Source: University of North Carolina at Charlotte