Scientists find gene for clotting disorder

People with venous thrombosis suffer from blood that forms clots aggressively. This week, Dutch researchers report finding a mutant gene that underlies this clotting disorder.

Researchers had long known that venous thrombosis runs in families. In people with the condition, blood pools in the veins of the legs, causing clots to form. Those jellylike clots can cause pain, inflammation, and even death if they break off and travel to the lungs.

In February, a team of Swedish investigators discovered that the action of activated protein C (APC), a naturally produced anticlotting substance, seems to be blocked in people with a family history of this disorder.

That finding spurred the hunt for the genetic cause of this overzealous clotting. Biochemist Rogier M. Bertina of University Hospital in Leiden, the Netherlands, and his colleagues focused on chromosome 1, one of the 23 pairs of human chromosomes and a likely location for the faulty clotting gene. After comparing the DNA of family members whose blood formed clots normally to that of members whose blood clotted too much, the researchers found that the difference came down to this: Relatives with clot-prone blood showed a single mutation, or flaw, in the gene that codes for Factor V, a protein that dramatically accelerates the body's clotting process.

The Factor V that this mutant gene codes for is identical to the normal protein except for one thing: A single amino acid is out of place. That seemingly minor goof, like a typo in an otherwise clean manuscript, results in a souped-up Factor V. Normally, this factor helps the body form beneficial blood clots, such as those aiding in the repair of an injury. Once the clots have done their job, the body sends APC to destroy Factor V and thus dampen the clotting cascade. But for people with the genetic defect, there's no brake on this process. The mutant Factor V remains impervious to APC's attack. This results in blood that keeps on clotting long after it should have stopped.

Bertina suspects, but has yet to prove, that people who inherit two copies of the mutant Factor V gene show an even greater tendency to form clots than those who carry just one such gene.

The discovery of the flawed gene makes the Factor V defect the most common genetically determined clotting disorder, the authors write in the May 5 NATURE. About half the people with a family history of venous thrombosis carry the mutant gene, they say. Bertina estimates that 2 to 4 percent of the Dutch population carries it. The mutation probably occurs at the same rate in the United States, he says.

This high frequency suggests that the mutation conferred some evolutionary advantage upon people who inherited it, Bertina says. Perhaps those with a hypercharged clotting system were more likely to survive injuries, he speculates.

Although "remarkably" common, the flawed gene doesn't underlie every case of venous thrombosis, points out Kenneth A. Bauer of Harvard Medical School in Boston. Other genes, as well as environmental factors, probably contribute to an individual's risk of developing these blood clots, he says.

Clinical applications of this genetic find are unclear. Most people who carry the mutant gene will never suffer from a dangerous clotting episode, asserts hematologist Philip W. Majerus at the Washington University School of Medicine in St. Louis. Physicians have yet to devise a foolproof method of preventing clots from forming or identifying people at high risk of developing such blood clots.

"Thus the risks of lifelong treatment with anticoagulants must be weighed against the benefit of preventing infrequent, but potentially devastating, thrombotic attacks," Majerus writes in a commentary that accompanies the Dutch report. *– K.A. Fackelmann*

Watching polymers wend their way along

How do polymers really move?

Do the long, chainlike molecules float through solutions in a haphazard way? Or do these tangled tubes tend to wriggle through viscous fluids like small snakes slithering through mud?

These questions have puzzled chemists for decades, especially since the "reptation" model appeared in the early 1970s. This theory holds that polymers undulate as they meander through matter.

What has hamstrung chemists trying to test this model thoroughly has been a lack of direct visual evidence. Until several months ago, no one had actually seen a single polymer slither. Then, in the March 17 NATURE, a group of scientists reported seeing the squiggling motion of actin filaments.

Now, Thomas T. Perkins, Douglas E. Smith, and Steven Chu, all physicists at Stanford University, describe observing the wriggling of a single strand of DNA. Their report appears in the May 6 SCIENCE.

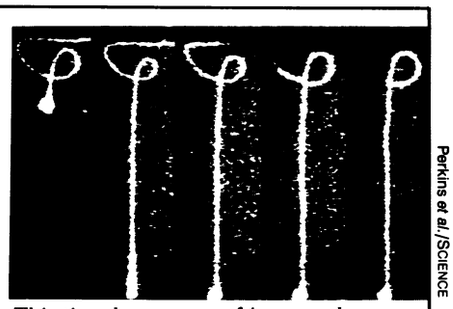
Using fluorescence microscopy and stained DNA, the scientists first watched individual DNA strands contort in ways predicted by the reptation theory, then tracked the molecule's twists and turns for up to 2 minutes at a time.

With optical tweezers, a laser method that enables them to manipulate individual DNA strands, the researchers tugged and twisted one strand at a time, deforming it in various ways. "We'd grab it, pull it, and watch it move," says Perkins. "We made a loop and pulled on one end. Then we squeezed it and watched it expand back." One by one, bends, kinks, and loops took hold. Then, as the strands relaxed, the researchers tracked the uncurling and unwinding.

"Now that this behavior can be seen – things like tube deformation and elasticity – it's no longer considered speculative," Perkins adds.

Among the more interesting properties of some polymers is "viscoelastic" behavior, Perkins points out. The taffy-like plastic known as Silly Putty provides a good example. When slowly stretched, it moves like molasses. When quickly compressed, it bounces back like rubber. When pressurized, it can behave like glass.

This intriguing blend of behaviors is explained by the reptation model, which suggests that each molecule moves within certain limits – sort of like a string of pearls sliding through a tube. Each pearl must travel alongside its neighbors, constraining the overall movement.



Perkins *et al.*/SCIENCE

This timed sequence of images shows a looped DNA strand unwinding.

But this seemingly simple theory has turned out to be quite difficult to prove, says Chu. To study polymer motion, most experimenters have focused on the properties of large lumps of polymer rather than the motions of single chains.

Yet such "bulk" experiments "can be misleading," Chu says.

"Confirming the reptation model took so long because many bulk experiments didn't end up testing what we thought they were testing," Chu says. "Maybe now that people can directly visualize individual moving molecules, some questions will become clearer. This really is a different way to do polymer science." *– R. Lipkin*