bers who are carrying the Huntington's disease gene but do not know it. They have not yet told the American family that they were the ones whose cells were used in this project. And they did not publish all of their data on the Venezuelan family in the *Nature* paper, writing instead, "Although a number of younger at-risk individuals were also analyzed as part of this study, for the sake of these family members the data are not shown due to their predictive nature. The data are available upon request if confidentiality can be assured."

The next steps scientifically are a bit easier. The first thing to do, says Gusella, is to check more families to see whether there are other Huntington's disease genes elsewhere on the genome. Next, they want to get more restriction enzyme markers, including ones on either side of the gene, that will allow them to zero in on it. What this does, says Housman, is to narrow down the outer limits of where the gene can be. "We may get down to 500,000 base pairs. Then we will work through that trying to figure out what relates to the disease."

But how do you go from a 500,000 base pair region to the isolation of a specific gene when you have no idea what the gene looks like or what it does? "That question is really at the cutting edge of science right now," Housman says. "I can give you five or six ways we can try but I can't give you a simple answer." Basically, however, there are two approaches. Researchers can take a functional approach, asking what kinds of RNA's are coded by the region, then figuring out what proteins are made and asking whether any of these might be associated with Huntington's disease. Or they can take a genetic approach, precisely comparing the DNA in this region and looking for a difference between unaffected persons and carriers of the Huntington's disease gene. In any event, the investigators expect that it will take years before they actually isolate the gene and find out what it does.

But the difficult work ahead of them in no way diminishes the researchers' enthusiasm. This is the first time anyone has used restriction enzyme markers to locate a gene that could have been anywhere on the genome. Always before they at least knew on which chromosome to begin looking. And although they always thought the restriction enzyme techniques would eventually lead them to the Huntington's disease gene, everyone thought that it would take at least 5 or 10 more years. "It is shocking but it's wonderful," Wexler says.

—GINA KOLATA

Viroid Origin in Jumping Genes?

Viroids are the smallest known infectious agents, which so far have been shown to occur only in plants. They are single-stranded RNA molecules and typically are from 270 to 380 nucleotides long; this is at least three orders of magnitude smaller than even the most diminutive virus. Unlike viruses, viroids are naked: the RNA strand is not encapsulated in a protein coat. Despite many attempts, no one has found a viroid-encoded protein: the genome, it seems, might not be translated at all. Viroids, clearly, are mysterious beasts. Recent analysis of nucleotide sequences of one group of viroids has, however, given a possible glimpse into the origin of these enigmatic pathogens. Theodore Diener and his colleagues at the Plant Protection Institute, Beltsville, Maryland, report features in viroid sequences that echo structural aspects of transposable genetic elements.*

In addition to encoding certain essential aspects of their insertion into and excision from their host genome, transposable elements often carry other potentially active genes. Because of many structural similarities between transposable elements and retroviruses, in particular certain sets of direct and inverted repeat sequences, there is now wide agreement that these RNA viruses evolved from mobile elements, presumably, among other things, by adding groups of cellular genes to the mobile unit. The life cycle of retroviruses includes reverse transcription into DNA, which becomes integrated into the host genome. By contrast, viroids might have derived from transposable elements by the loss of internal coding regions and the deletion of sections of the so-called long terminal repeats (LTR's). Moreover, viroids do not pass through a DNA stage in their life cycle: they are replicated directly as RNA, by an as yet to be determined host enzyme, and are not integrated into the host genome.

When Michael Kiefer sequenced tomato planta macho viroid and tomato apical stunt viroid earlier this year, he saw that they were related to three others that formed the potato spindle tuber viroid group. Kiefer, together with Diener and Robert Owens, was therefore able to look for sequence patterns within the group and with other organisms. One stretch of 28 nucleotides, located around position 100, is identical between the five viroids, and a second stretch, around position 320, is virtually so. Because the single RNA strand of viroids is often covalently linked as a closed circle, the overall structure may conform to a stiff "rod," which is held together by extensive base pairing so typical of viroid sequences. This arrangement happens to bring the two highly conserved regions opposite one another, forming what has become known as the conserved center.

The significance of the conserved center is that in the upper strand the sequences are formed from two more or less complete direct repeats, which are flanked by somewhat incomplete inverted repeats; the dinucleotides CA and UG also flank the direct repeats. These patterns, which are echoed imperfectly in the lower strand of the viroid loop, are very similar to structural features of LTR's in transposable elements but with certain sections deleted. In addition to the repeats in the central section of the viroids, there appear to be many remnants of inverted repeats scattered throughout the body of the molecule.

Another feature common to the potato spindle viroids is a stretch of 11 to 18 uninterrupted purine bases centered on position 60. Such a signature is reminiscent of the putative signal site for reverse transcriptase activity in retroviruses. Its presence in viroids, which apparently do not make DNA copies of themselves, might bespeak a common origin with retroviruses. The site might have become modified for initiating RNA synthesis.

If viroids do indeed derive from transposable elements one would expect to see somewhere in the host genomes at least some sequences similar to those of the viroids. So far no one has found such sequences, but searches have been made in the commercially important plants in which viroids cause pathologies rather than in wild plants in which they originated. Diener plans soon to shift the search to these wild plants.—ROGER LEWIN

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