Navigating the human genome with Sequins

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Australian genomics researchers have announced the development of Sequins—synthetic 'mirror' DNA sequences that reflect the human genome. This intuitive new technology, which can be used to better map and analyse complexity within the genome, is freely available to the academic research community.

The human genome is a vastly complicated sequence that contains more than 6 billion DNA 'letters' (the bases A, C, G and T). Although we can now sequence a person's genome relatively cheaply and quickly, the subsequent analysis of the human genome is a much deeper and more difficult problem.

In a bid to improve the quality of genomic analysis, scientists at Australia's Garvan Institute of Medical Research have developed a new technology based on synthetic human genome sequences called 'Sequins'. The Sequins technology is described in two linked studies published today in the prestigious scientific journal *Nature Methods*.

"Human genome sequencing is transforming biomedical research and healthcare," says Dr Tim Mercer, of Garvan's Genomics and Epigenetics Division, who led the development of Sequins.

"And as genome sequencing is being increasingly used to diagnose disease, it is more important than ever that researchers and clinicians understand the accuracy of the genomic data they are looking at."

Dr Mercer and his team came up with the idea of adding Sequins, small

stretches of synthetic DNA, to a patient's DNA sample during sequencing. These Sequins (or sequencing spike-ins) then act as internal standards, helping researchers analyse the large data files that are generated during genome sequencing.

Dr Mercer says the Sequins technology is based on an intuitively simple concept—the notion of mirror-image DNA.

"Sequins are, essentially, mirror images of natural DNA sequences. Like us, the genome has a 'handedness', and just as our right hand differs from our left hand, sequins differ from natural genome sequences. So sequins behave just like natural genome sequences, but they can be easily recognised as synthetic."

When added to a sequencing reaction, sequins provide internal controls with which to assess the sensitivity and accuracy of genome sequencing.

Dr Mercer says, "A whole series of steps, first in the lab and then on the computer, are required to sequence a person's genome or the genes that are expressed in different cells. Sequins are with the person's DNA every step of the way: responding just as real DNA does at each step, yet unmistakably different from that real DNA. This allows a scientist to assess, and optimise, these different steps."

Because sequins are added to each individual sample, they can provide a sample-by-sample assessment - something that has not previously been possible.

"Sequins are the first technology to allow diagnostic statistics to be applied to each individual genome sequencing test," Dr Mercer says, "and we anticipate that their use will improve the reliability and sensitivity of genetic disease diagnosis."

Cancer diagnosis is one area in which using Sequins should lead to improvements.

"Incorporating Sequins into clinical tests for cancer diagnosis will increase the reliability of an individual diagnostic readout, reducing incorrect diagnoses and giving clinicians greater confidence in deciding the best course of treatment for their patient."

Using Sequins will also make it possible to directly compare genomic data from research institutes and sequencing centres worldwide.

"Sequins bring DNA sequencing to clinical standard, and will be an essential platform for genomic research and medicine," said Garvan's Executive Director and co-author of the studies, Professor John Mattick.

The potential applications of Sequins are many. Because all genomes, from bacteria to human, have handedness, sequins can be similarly designed for any organism, or for almost any next-generation sequencing application.

Dr Mercer says that Sequins technology is freely available to other researchers.

"We invite academics to get in touch and we can send them some Sequins for their genome research. We're keen to get this technology out into other labs, in Australia and worldwide."

"This is another important step in advancing Garvan's mission to bring genomics to the clinic," said Professor Mattick.

More information: *Nature Methods*, DOI: 10.1038/nmeth.3957

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