The Rise of Long Reads

Mike Snyder Says Long-Read Sequencing Is Critical to Understanding the Transcriptome

Genomics luminary Mike Snyder, Professor and Chair of the Genetics Department at Stanford University and Director of the Stanford Center for Genomics and Personalized Medicine, has been making strides in gene expression studies for years. His latest advance: analyzing whole human transcriptomes, which he calls personal transcriptomes, to better understand gene activity in an individual. Snyder says this approach could one day become a crucial element in clinical care. Dr. Snyder has published recent papers in Nature Biotechnology and PNAS using Single Molecule, Real-Time (SMRT®) Sequencing for transcriptome analysis and demonstrated that long reads enable full coverage of RNA molecules.

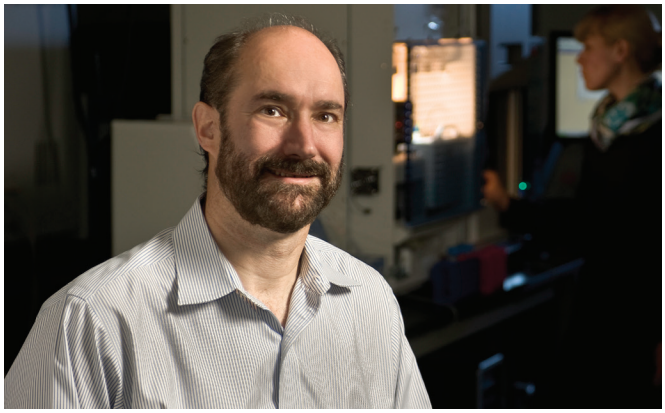
Recently he talked to Mendelspod host Theral Timpson as part of a series of podcasts on the rise of long-read sequencing.

On the State of Transcriptomics

Without using long-read sequencing, the way transcriptomes are figured out is "crazy," Snyder explained. "We take RNA, we blow it up into little fragments, and then we try and assemble them back together to see what the transcriptome looked like in the first place. And that's a horrible way to do this because what we're really trying to do is understand all of the different isoforms of a transcript....So when you blow them up and try to reassemble them back together you can't always figure out which parts of the puzzle belong together."

The Power of Long-Read Sequencing

By nature, long-read sequencing can avoid 'blowing up' the transcripts, because as Snyder has demonstrated in his studies, it is possible to generate full-length transcripts using SMRT Sequencing. "The power of long-read sequencing is really to be able to capture all of the information in its intact form without trying to solve a jigsaw puzzle that you may have put together wrong." Snyder explained that misassembling transcripts can make it impossible to understand what is going on. For example, different isoforms of the same tumor gene have very different functions and may be either healthy or oncogenic.



On the $1000 genome

"Has the race to the $1000 genome been at the expense of quality?" Timpson asked Snyder. "Yes," he replied. "I think people's eyes are opening to that." Based on what is currently considered the "$1,000 Genome" (which Snyder points out cannot actually be commercially purchased today for $1,000), he said, "the quality is still not there, there's still significant gaps."

"People don't realize this but there are still several hundred gaps in the human genome that have never been closed," Snyder explained. And, ironically, in the process of attempting to fix these gaps in the reference genome, researchers end up uncovering more errors, "so the number of gaps in the human genome has stayed fairly constant over the last 10 years or so," he adds.

Snyder believes that PacBio's SMRT Sequencing provides one solution to this problem, by spanning gaps, resolving structural variation and providing the 'gold standard' in quality in sequencing today.

The full interview can be found at www.Mendelspod.com

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References

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Sharon et al. (2013) A single-molecule long-read survey of the human transcriptome. *Nature Biotechnol 31*, 1009-1014

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