

Seeing the Forest for the Trees: Critiquing Genetic Theory



Henry Heng, PhD.

Dr. Henry Heng, Associate Professor of Molecular Medicine and Genetics and of Pathology, is taking a unique approach to genetic theory. According to Heng, modern genetics might need a complete overhaul to understand the complex workings of the genome.

Heng says that geneticists have focused far too much on individual genes and not enough on the genome as a whole. Genes, he says, only represent parts of the genetic system and are fundamentally different from the entire genome. "A list of materials needed to build a building does not instruct builders how to make that building," Heng says. He proposes that genome context, which is made by not only the information coded in DNA sequences but also the information hidden in the genome topology, is the key to complex diseases such as cancer.

Traditionally, in looking for the cause of complex diseases, geneticists have looked at individual genes. As technologies have advanced, scientists have moved to looking for defects in all of the 20,000 genes in the human genome and trying to find a consensus pattern of gene mutations and a pattern of alteration of the pathways that those genes function in for each type of cancer. However, Heng says that the full answer is not in mutations of specific genes or pathways, as most cancer patients do not share the same gene mutations. Instead, Heng focuses on large scale genome change such as chromosomal rearrangements and changes in the number of chromosomes, as these changes are nearly universal in cancer.

He explains that the difference between the traditional view of genetics and his genome theory is that traditional gene based genetics is like looking at two different houses, systems, and blaming

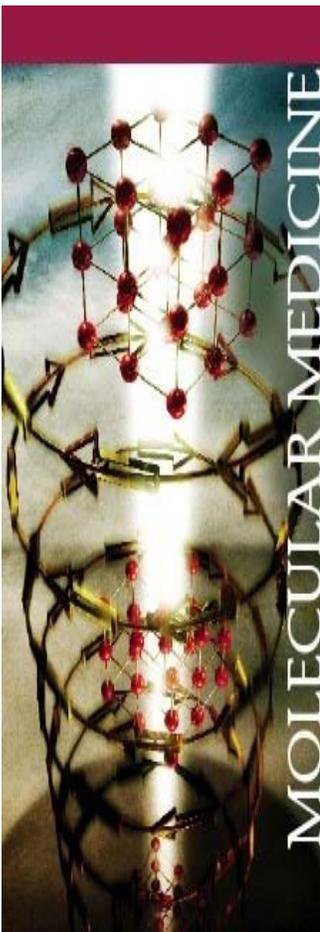
a few bricks for the differences in architecture. Instead, the entire genome, the whole house, needs to be studied.

Heng says his group first considered this line of thinking while studying gene and chromosome change in cancer models. "Traditional models of cancer say that we should find a straightforward, stepwise pattern of gene and chromosomal change," he says, "but what we found was something far different. We found that the genomic makeup of cancer cells was changing randomly and sometimes very rapidly." He observed that specific genes were contributory in some isolated exceptional cases, but the common mechanism of cancer progression was evolution driven by random chromosome change, which he calls 'genome replacement mediated macro-cellular-evolution.' This led his lab to believe that cancer is a disease of the genome rather than individual genes.

Recently, Heng has also observed that in cells subjected to stress, chromosomes, actually break apart and rearrange themselves in different, often complex, random combinations in a process called genome chaos, possibly causing a variety of diseases, including cancer, and driving resistance to treatment. "The ability of the cancer genome to adaptively evolve is incredible," Heng says with an air of remorse, "If cancer followed the stepwise models of progression, we would be much better at treating it."

Unsurprisingly, the scientific community at large initially had a hard time accepting Heng's theories. However, this has not dissuaded Heng. He understands that it will take time, and a great deal of study, for his theories to take root. Following 10 years of fighting the mainstream, his viewpoints are now catching on. In addition to participating in various think tank meetings, his group has been frequently invited to write perspectives and book chapters, as well as editing special issues for different journals.

Heng will be publishing a book titled "4D-Genomics: Genome Dynamics and Constraint" later this year to introduce his genome theory.



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