

## WHY SO MANY DIFFERENT TRANSCRIPTS

When the Human Genome Project was nearing completion, expectations were high. How many genes does *Homo sapiens* carry? Estimates ranged from 80,000 to 150,000, with some voices pushing toward 200,000. The reasoning was intuitive: we are complex, we are unique, our genome must reflect that. The answer was deflating: somewhere between 20,000 and 25,000 protein-coding genes. About the same as a mouse. Not far from a worm.

Biology quickly found a way to restore our sense of exceptionalism. Never mind gene number. Human cells produce a remarkable diversity of transcripts through alternative splicing. We might share the same gene catalogue as a rodent, but we were running far more sophisticated software on the same hardware. Complexity rescued from the jaws of humility.

Then came ENCODE. In 2012, the project declared that roughly 80% of the human genome shows biochemical activity and should therefore be considered "functional." The concept of junk DNA was pronounced dead. Everything was there for a reason. A new paper by Mi et al., published in PLOS Biology [(1), and a commentary (2)], adds another chapter to this recurring story. The question is simple: why do large-bodied species like humans have so many alternative transcripts? The answer is not flattering. Most of that transcript diversity is molecular noise, errors in RNA processing that natural selection is too weak to eliminate.

The explanation comes from population genetics. Species with small effective population sizes, and humans qualify because we are large, long-lived, and slow to reproduce, experience weaker natural selection. Mildly harmful errors accumulate not because they are useful, but because chance overwhelms selection. Mi et al. show, across 67 animal species, that transcript diversity scales predictably with small population size. And the extra transcripts look like mistakes because they are mistakes: they are rare, carry weak splice sites, and contain premature stop codons.

What is striking, looking back, is how persistent our tendency is to read molecular complexity as a mark of distinction. Each time genomics has handed us a mirror, we have found a way to see confirmation of our uniqueness. And each time, a more careful evolutionary reading has suggested a simpler, less flattering explanation.

1. [10.1371/journal.pbio.3003671](https://doi.org/10.1371/journal.pbio.3003671)
2. [10.1371/journal.pbio.3003686](https://doi.org/10.1371/journal.pbio.3003686)