A SURPRISE ON THE SHORT ARM OF ACROCENTRICS

For decades, we've assumed that ribosomal DNA (rDNA, located on the short arms of acrocentric chromosomes) was just a massive cluster of identical cistrons, where the only thing that mattered was the number of copies.
It turns out we were missing a huge piece of the puzzle.
A groundbreaking study in Cell Genomics [(1), based on the UK Biobank] has found that the sequence of those copies varies too, in ways that are heritable and meaningful for human biology. The Expansion Segment 15L (ES15L) is the focal point of the paper.
ES15L is an insertion specific to eukaryotes, greatly expanded in hominids and, very interestingly, the human variants are absent in other great apes, are not identical across individuals, and are stably inherited. These variants are actively incorporated into functional ribosomes.
Most surprisingly, the frequency of these ES15L variants, what researchers call Intragenomic variant Frequency (IGF), is significantly associated with body size traits, specifically height and weight.
In summary, a genomic region routinely excluded from standard variant-calling pipelines turns out to harbour heritable sequence variation that reaches into ribosomes and correlates with how tall you are. The overlooked corner of the genome just got considerably more interesting.

Just a few days after this publication, a paper by Ma et al. in PNAS (2) adds a crucial piece of context; one that, at first glance, might seem to contradict the findings above, but in fact deepens them considerably.
The rRNA genes were long believed to be too important to vary: any mutation in those sequences would presumably cripple the ribosome. Ma et al. confirm this intuition with hard evolutionary data. Analysing the rDNA of over 3,000 individuals from the 1000 Genomes Project, they demonstrate that strong purifying selection actively suppresses the amplification of variants in the conserved core of the rRNA , the 18S, 5.8S, and the structurally essential elements of the 28S. Deleterious variants are eliminated even when present in just a handful of copies, which is precisely why no rRNA variant has ever been linked to a Mendelian disease: these variants simply cannot accumulate to frequencies detectable by standard methods.
But here is where the two papers connect with unexpected elegance. Ma et al. also show that the expansion segments, those evolutionarily young, protruding loops that extend from the ribosome's surface, are relatively permissive for variation. They are hotspots of rDNA diversity, less constrained by purifying selection because changes there are not immediately catastrophic for the ribosome's core function.
ES15L sits squarely in this permissive zone. It has expanded specifically in hominids, acquired human-specific sequence diversity (as Rodriguez-Algarra et al. show), and appears to have taken on new functional roles: modulating translation in ways that measurably influence body size. Together, the two papers describe the rDNA as a locus under a two-tier selective regime: an untouchable core held in near-perfect conservation across a billion years of evolution, and a periphery where human-specific variation is not only tolerated but phenotypically consequential. The overlooked corner of the genome turns out to have its own internal geography, and we are only beginning to map it.

1. https://www.cell.com/cell-genomics/fulltext/S2666-979X(26)00075-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2666979X26000753%3Fshowall%3Dtrue
2. https://doi.org/10.1073/pnas.2529741123