Cell Genomics

CellPress
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Article

Diversity of ribosomes at the level of rRNA variation associated with human health and disease

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https://doi.org/10.1016/j.xgen.2024.100629

Present via Lei, NIE

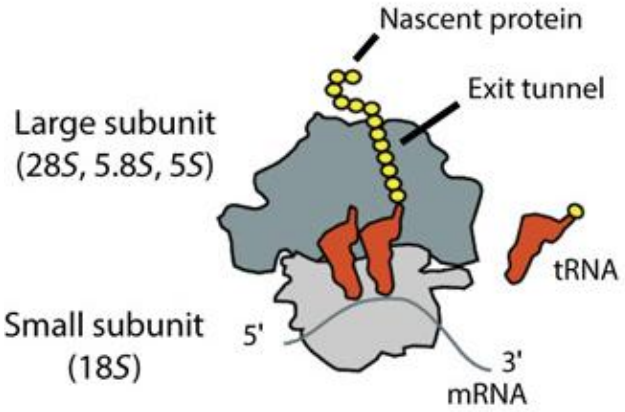
Maria Barna - Associate Professor of Genetics

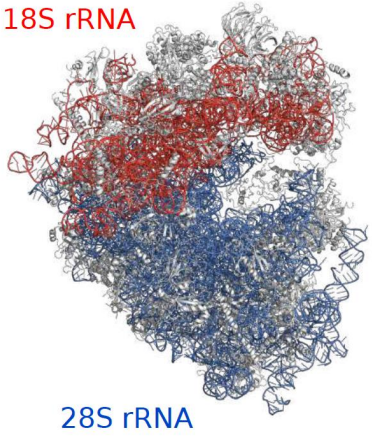
Bio-X Affiliated Faculty

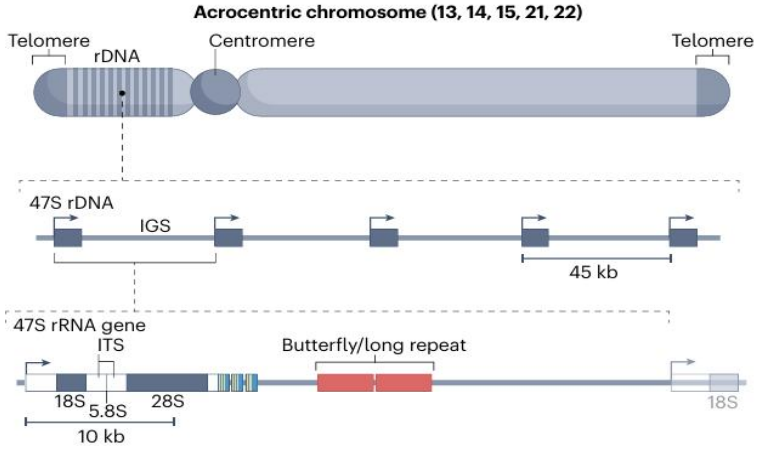
Stanford Profile | Dr. Barna's Lab Homepage

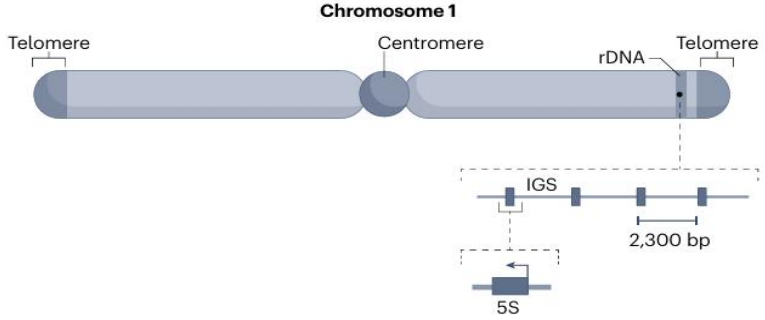
Dr. Maria Barna's lab studies how intricate control of gene expression and cell signaling is regulated on a minute-by-minute basis to give rise to the remarkable diversity of cell types and tissue morphology that form the living blueprints of developing organisms. This research aims to add a new dimension to our understanding of how cells "know" where to go, when to move and differentiate by employing novel technologies that probe these questions at a highly molecular and nanoscale level. Work in the Barna lab is presently split into two main research efforts. The first is investigating "specialized ribosomes" and mRNA translation in control of gene expression genome-wide in space and time during development. This research is opening a new field of study in which fundamental aspects of gene regulation are controlled by ribosomes harboring a unique activity that "select" for specific mRNAs to translate by virtue of unique RNA regulons embedded within 5'UTRs. The second research effort is centered on employing state-of-the-art live cell imaging to visualize cell signaling and cellular control of organogenesis. This research has led to the realization of a novel means of cell-cell communication dependent on a dense network of actin-based cellular extension within developing organs that interconnect and facilitate the precise transmission of molecular information between cells.

Background


Nascent protein
Exit tunnel
Large subunit
(28S, 5.8S, 5S)
tRNA
Small subunit
(18S)
5'
3'
mRNA

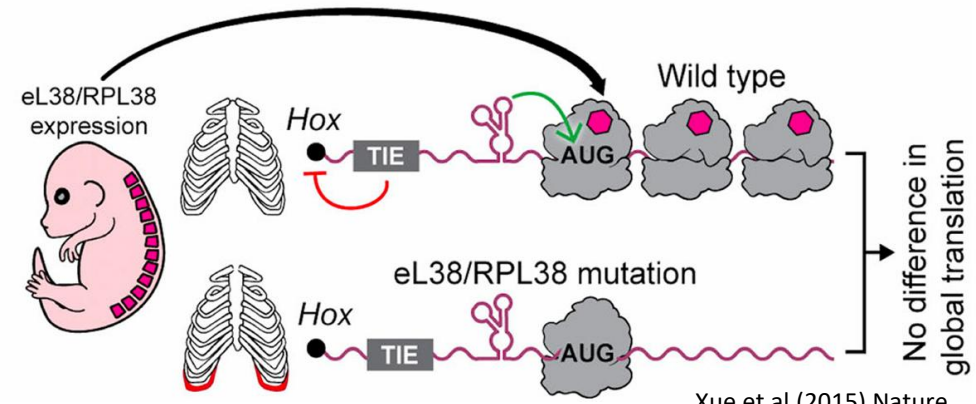

18S rRNA
28S rRNA


Acrocentric chromosome (13, 14, 15, 21, 22)
Telomere
rDNA
Centromere
Telomere
47S rDNA
IGS
45 kb
47S rRNA gene
ITS
Butterfly/long repeat
18S
5.8S
28S
18S
10 kb

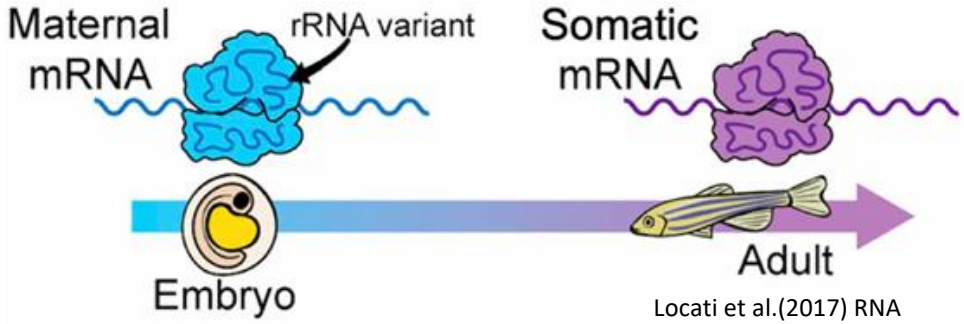

Chromosome 1
Telomere
Centromere
rDNA
Telomere
IGS
2,300 bp
5S

Background

ribosomes are heterogeneous



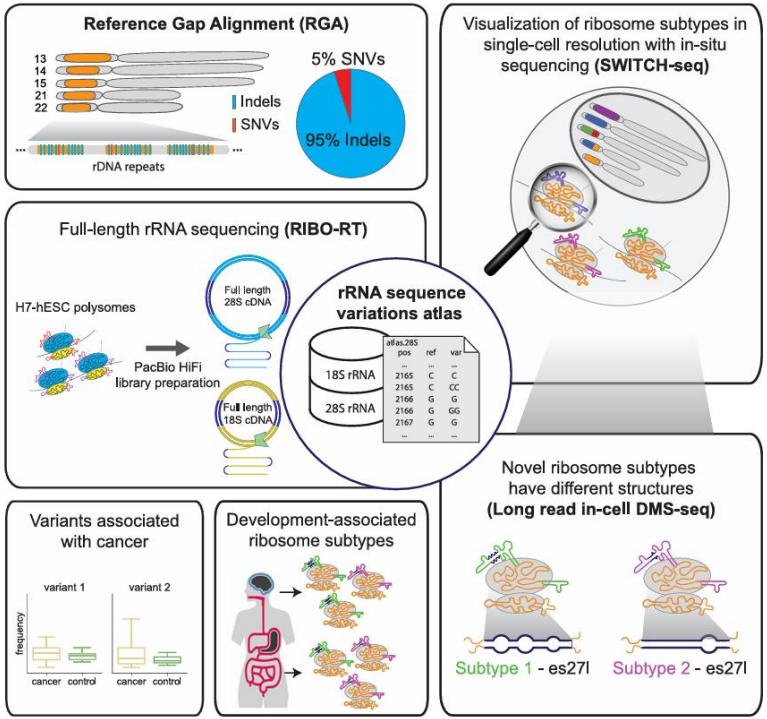
Xue et al.(2015) Nature



Locati et al.(2017) RNA

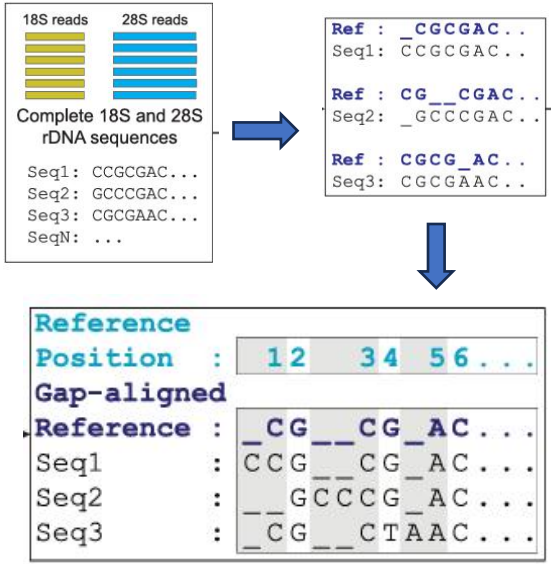
Inconsistent variant calling

Study	Dataset	Technology	SNVs	Indels
Parks et al. (Sci Adv, 2018)	1KGP	Illumina short-read	97.3%	2.7%
Fan et al. (RNA, 2022)	1KGP	Illumina short-read	80.8%	19.2%



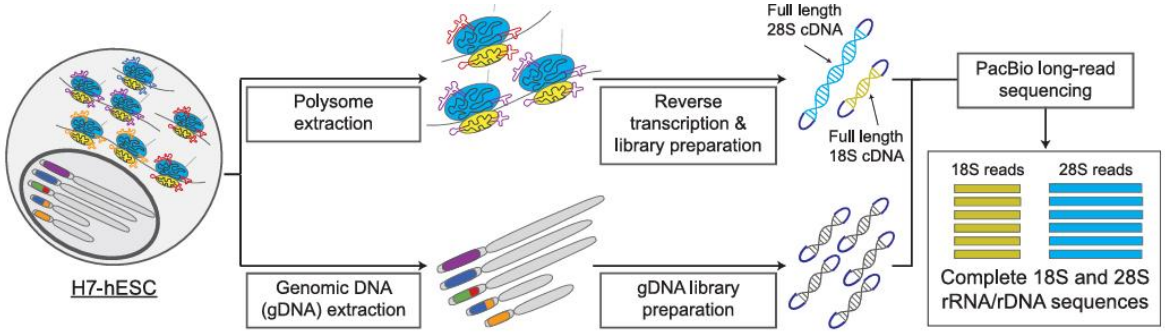
New pipeline for rDNA and rRNA variant calling

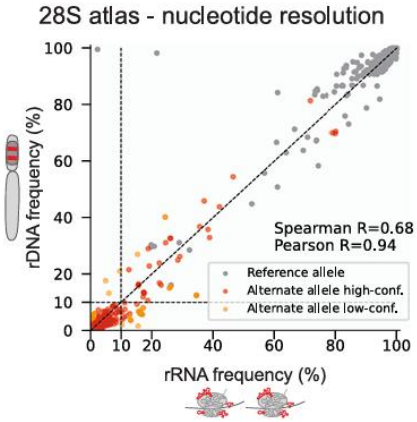
reference gap alignment (RGA) pipeline

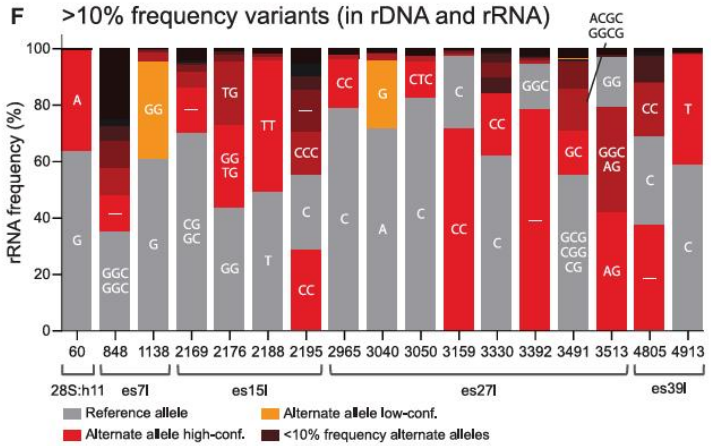


Dataset	Technology	SNVs	Indels
1KGP	HiFi long-read	5%	95%
GIAB	HiFi long-read	4%	96%

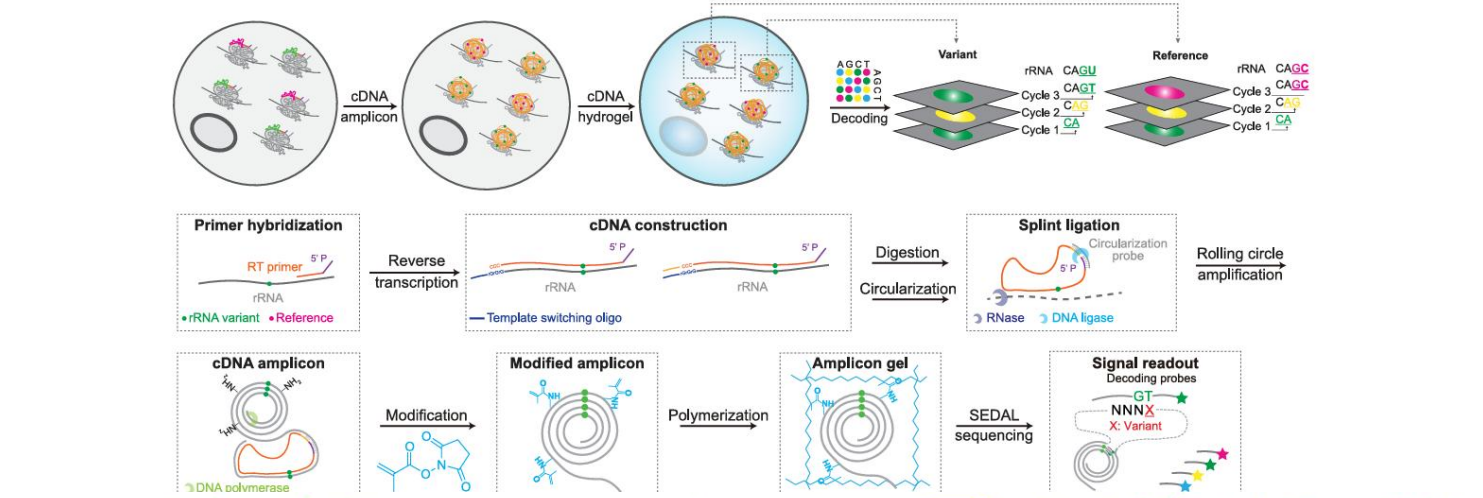
rDNA and rRNA variant calling showing co-expressed pattern

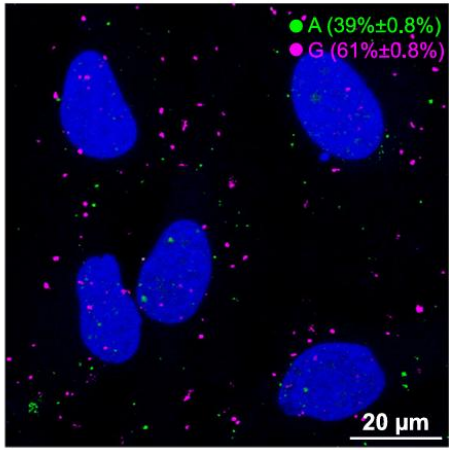




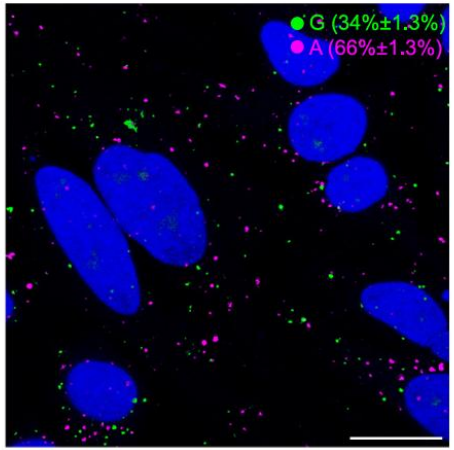


The co-expressed pattern visualized by *in situ* sequencing (**SWITCH-seq**)

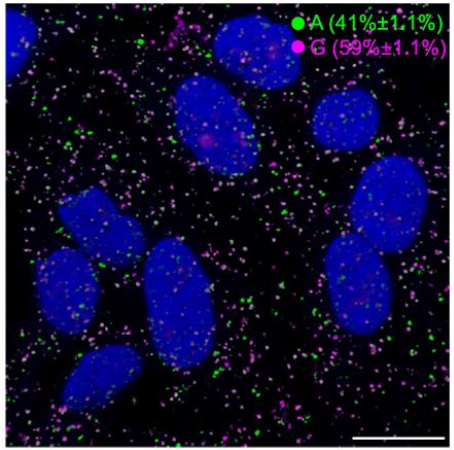




28S:h11 - position 60



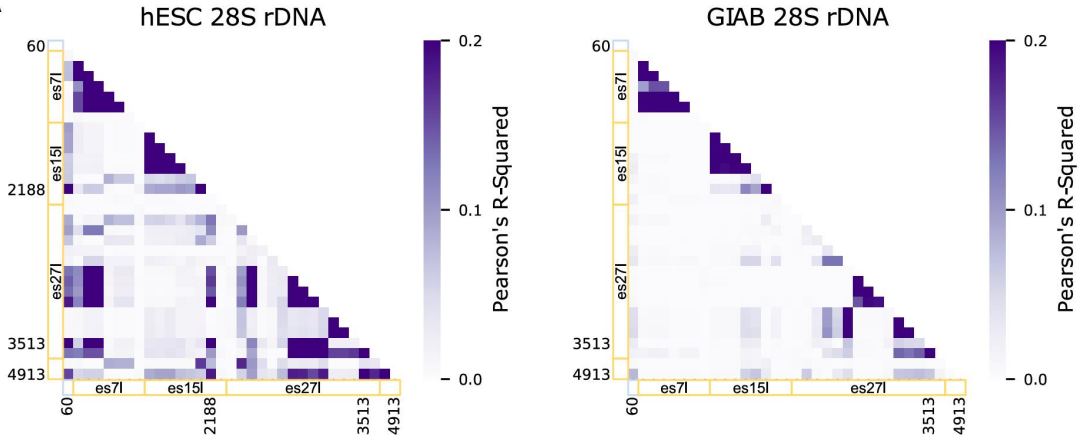
es27l - position 3040



es27l - position 3491

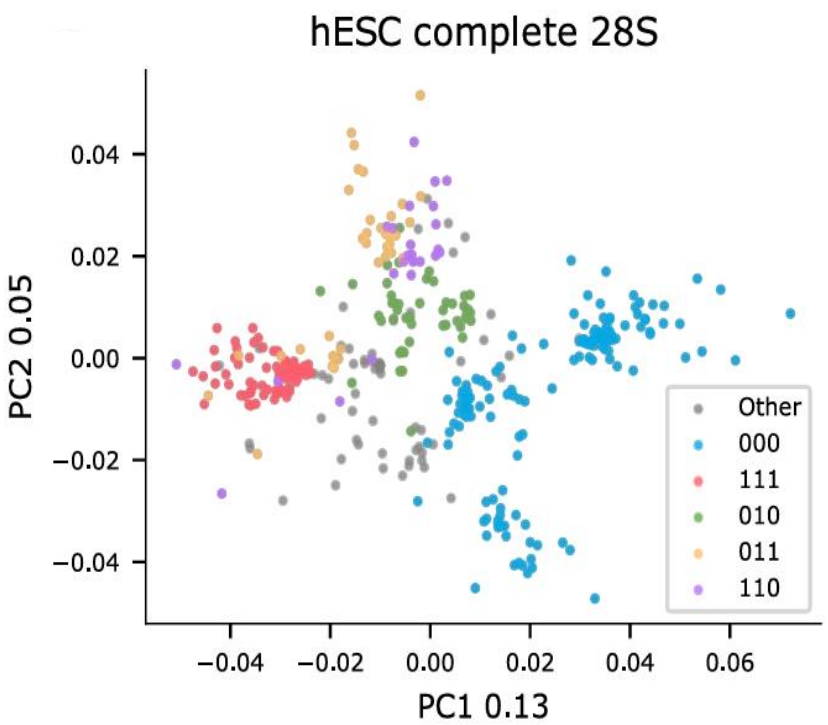
Three variants chosen for haplotyping the 28S rDNA

Association of Variants

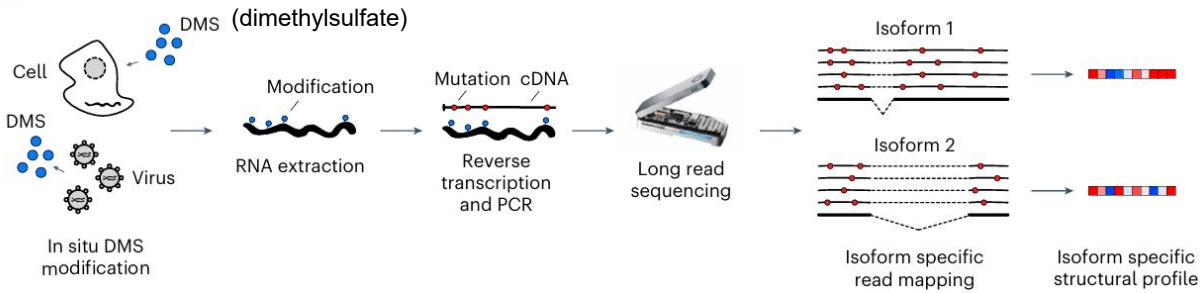


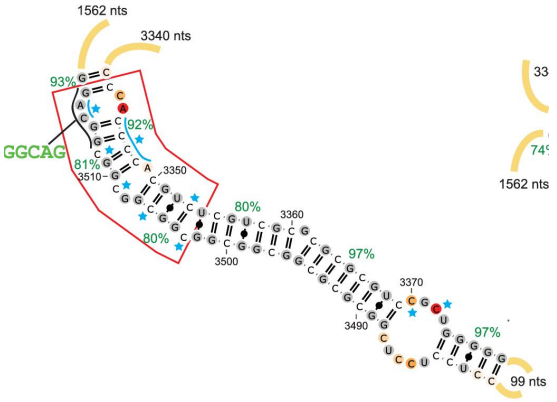
28S position	Digit	Nucleotide
60	0	G
	1	A
3513	0	AG
	1	GGCAG
	2	GG
4913	0	C
	1	T

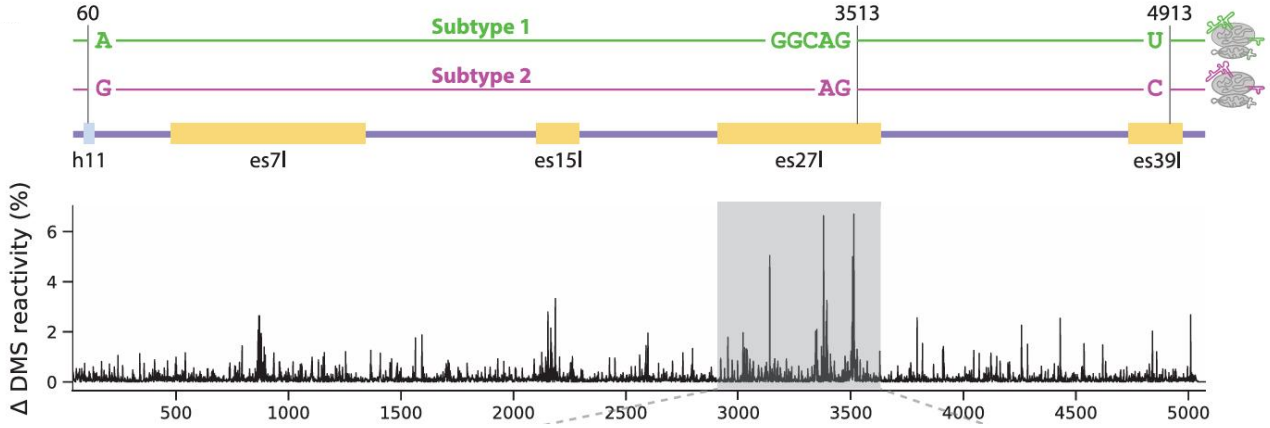
28S pairwise similarity in hESC

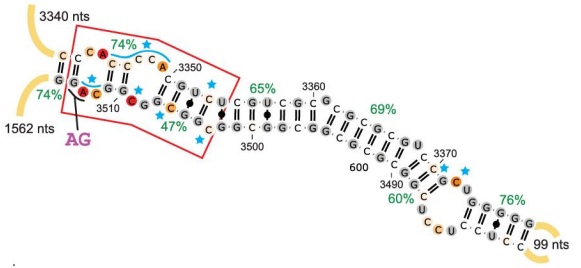


Variants leading to secondary structure difference



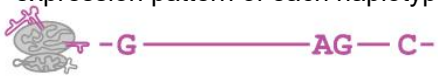


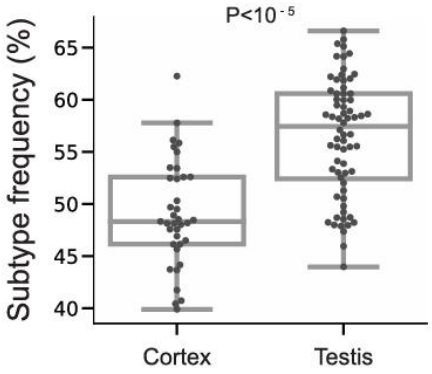


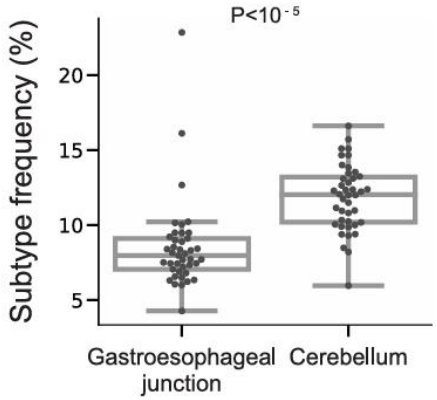


The relative abundance of rRNA variants in expression data

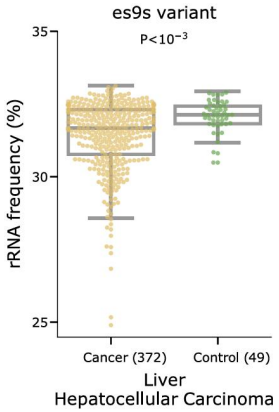
expression pattern of each haplotype is tissue specific

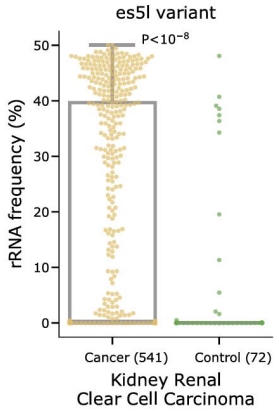


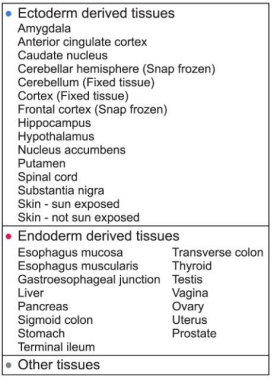


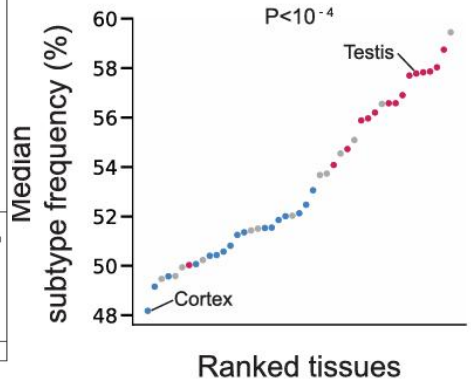


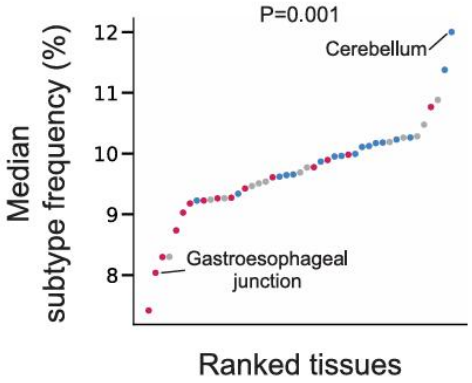
Some rRNA variants are cancer specific

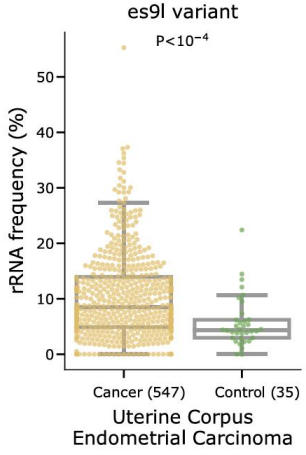


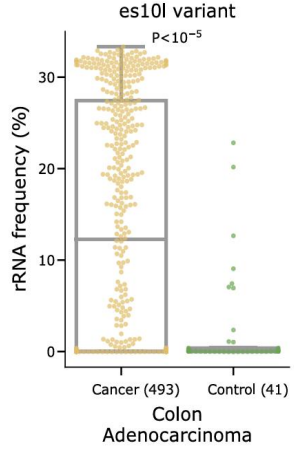












Conclusions

- New methods (RGA, RIBO-RT, SWITCH-seq) enable comprehensive study of rRNA variations.
- The rRNA subtypes show structural differences and tissue-specific expression.
- Some rRNA variants are linked to cancer.

Future Directions

- Can the subtype be determined just by one variant not a combination of variants
- Does the subtype frequency differences exist in different population, or in people of different ages.