

mRNA processing: misunderstood and underappreciated!

Yahya Anvar

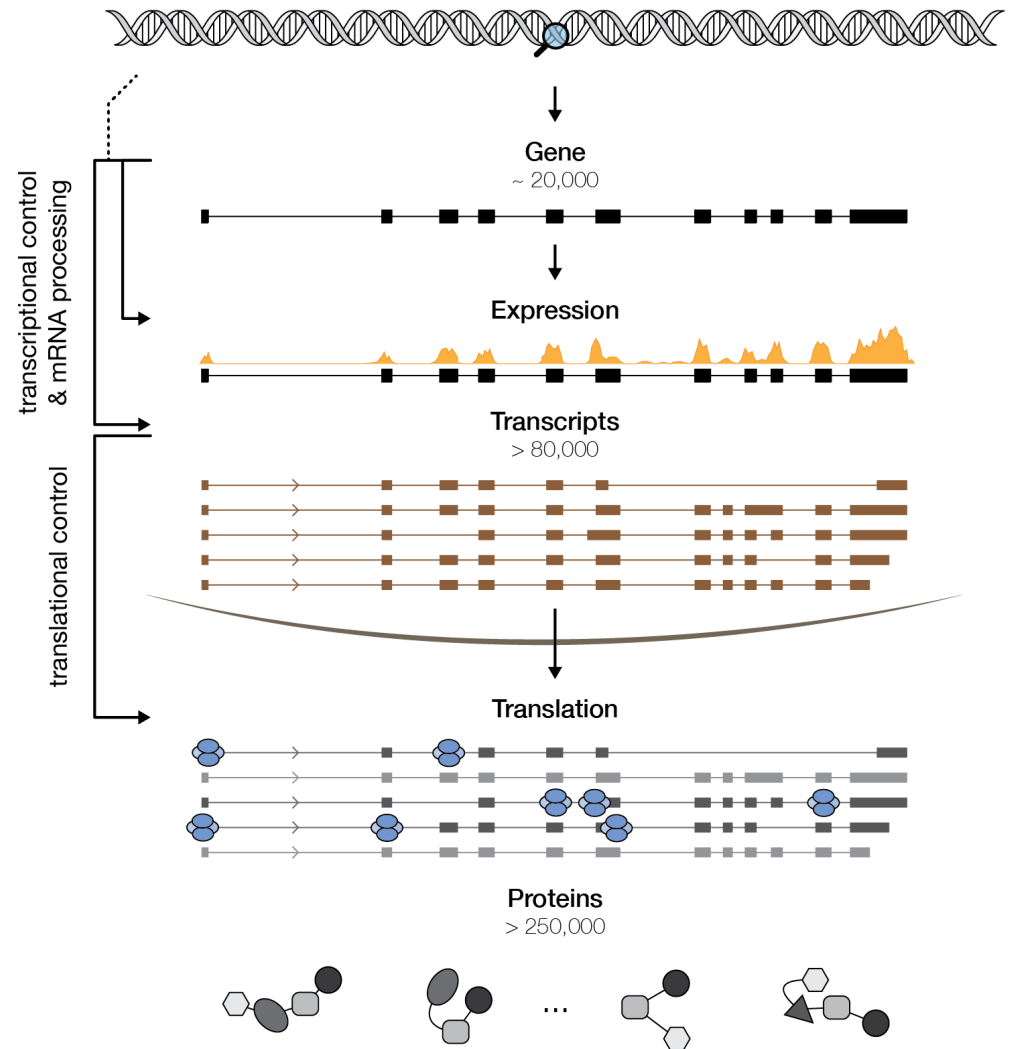
department of HUMAN GENETICS
department of CLINICAL PHARMACY AND TOXICOLOGY

“Nothing in the genome makes sense except in the light of transcriptome!”

– Tulli Lappalainen, NYGC

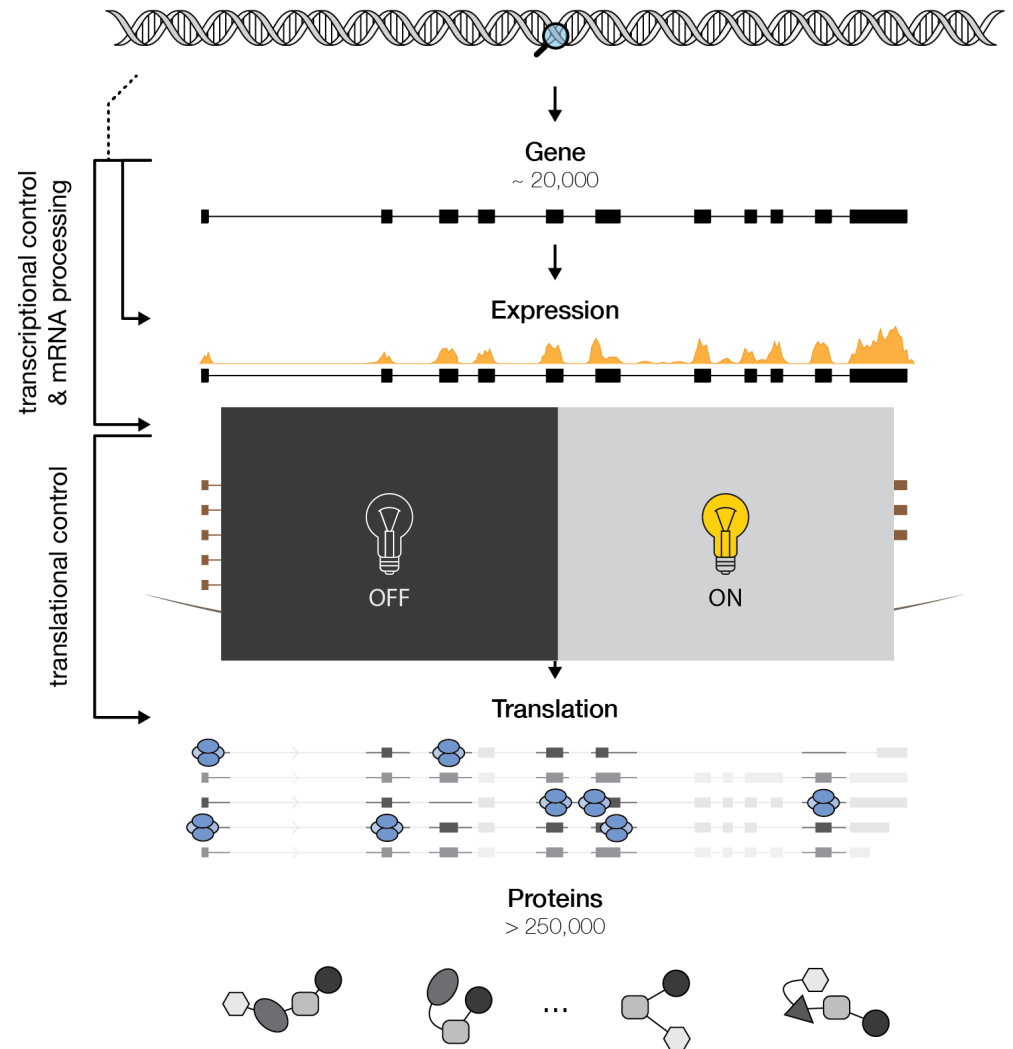
The number of protein-coding genes in vertebrates is not radically different from the number in invertebrates – from 20,000 human genes versus 19,000 genes in *Caenorhabditis elegans*. Thus, it is reasonable to assume that the prevalence of alternative splicing in vertebrates is important for their higher complexity.

Kornblihtt, AR et al. 2013

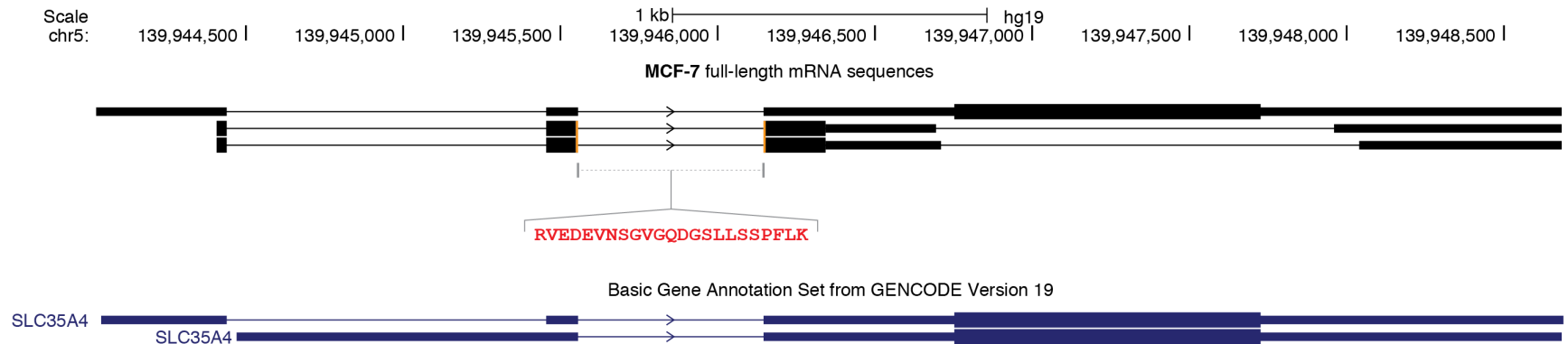


“Nothing in the genome makes sense except in the light of transcriptome!”

- Tulli Lappalainen, NYGC



“ To understand function,
 we can no longer ignore the
 shortcomings of short-reads! ”

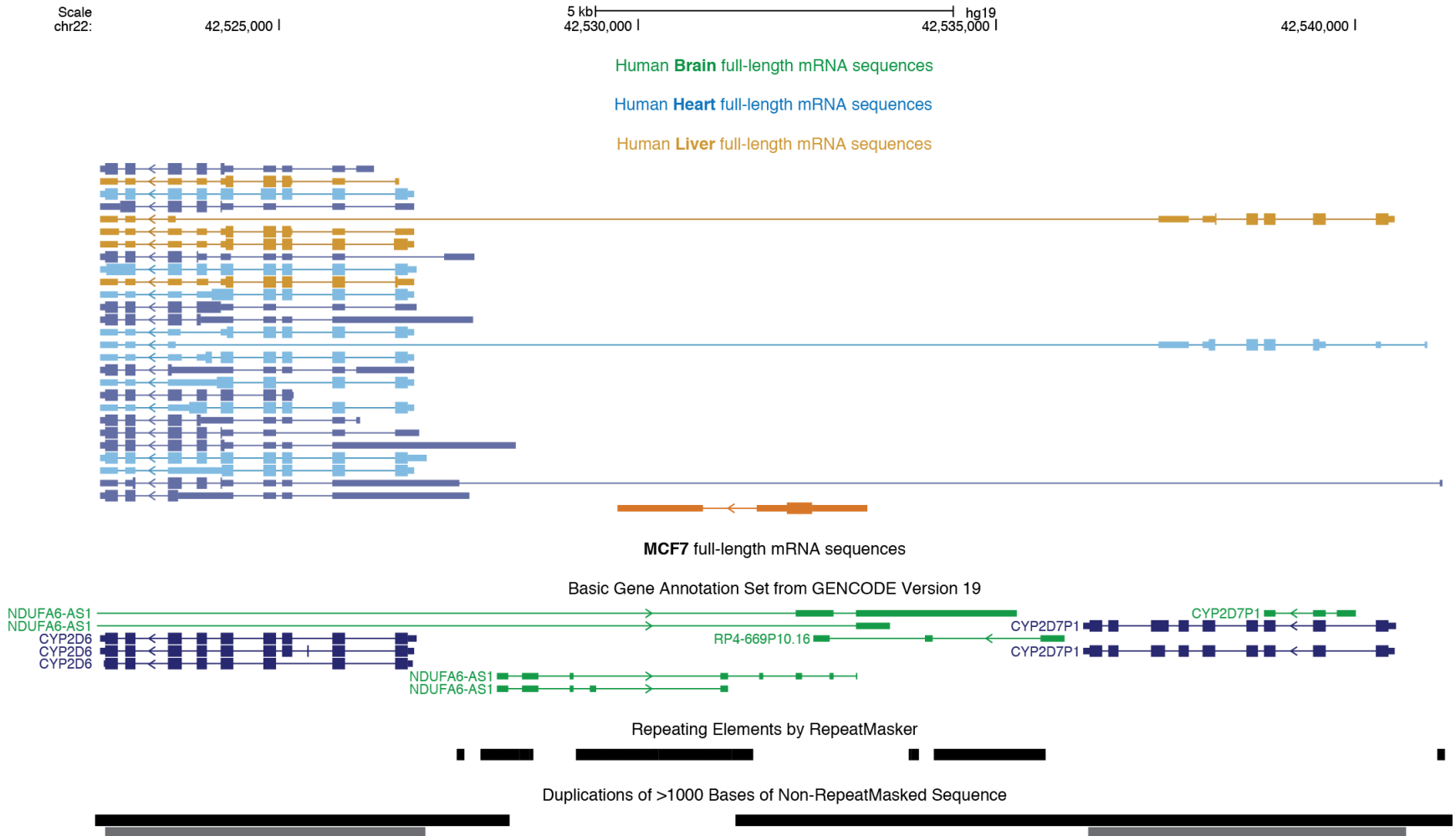


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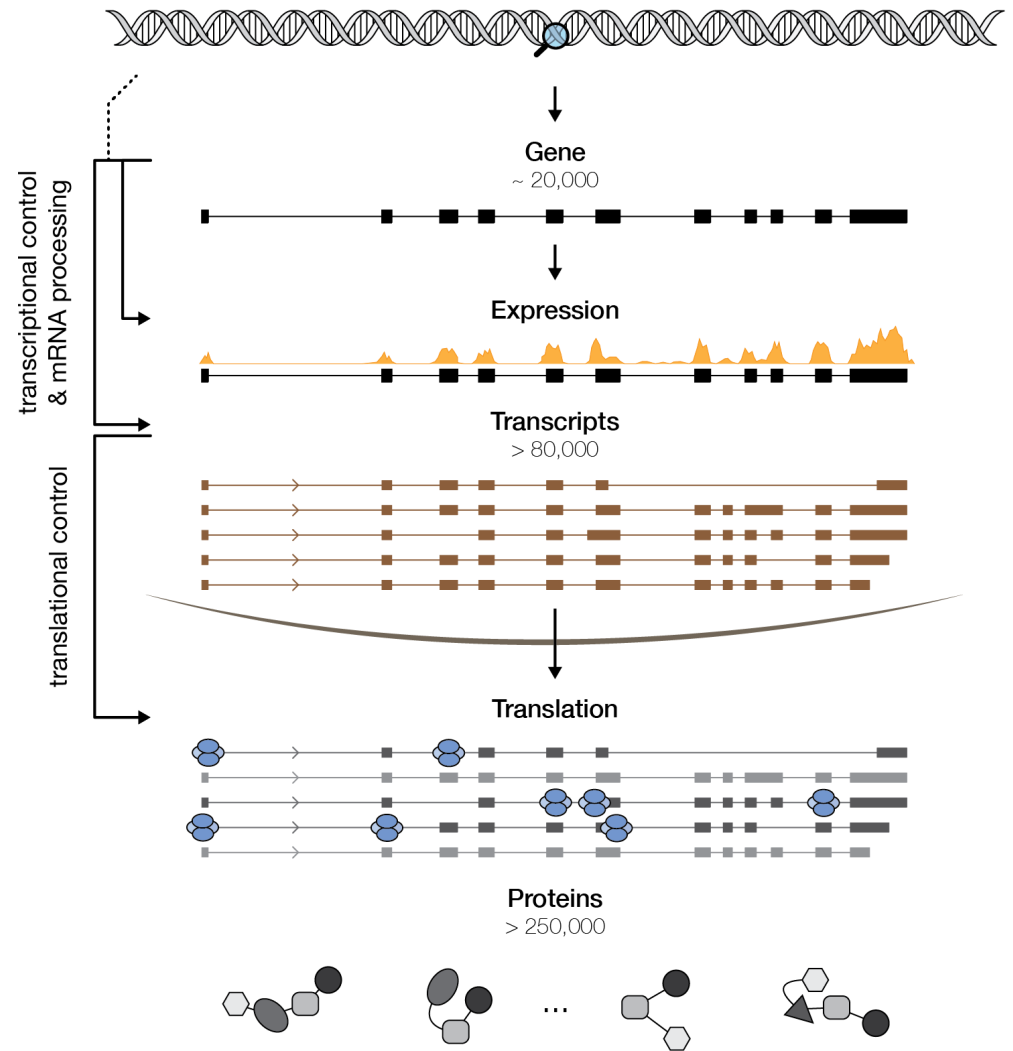
SLC35A4-02: WGSSAGKMADDKDSLPKLKDLAFLKNQLESLQR**RVEDEVNSGVGQDGSLLSSPFLK**GFLAGYVVAKLRASAVLGFVAVGTCTGIYAAQAYAVPNVEKTLRDYLQLLRKGPD*

SLC35A4-03: MGSSAGKMADDKDSLPKLKDLAFLKNQLESLQR**RVEDEVNSGVGQDGSLLSSPFLK**GFLAGYVVAKLRASAVLGFVAVGTCTGIYAAQAYAVPNVEKTLRDYLQLLRKGPD*

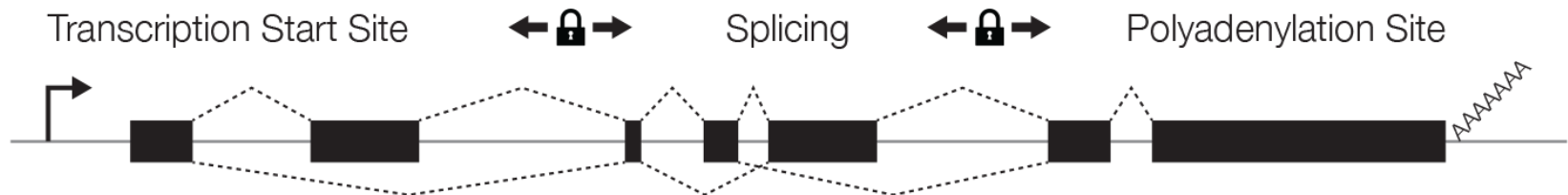
“ To understand function, we can no longer ignore the shortcomings of short-reads! ”



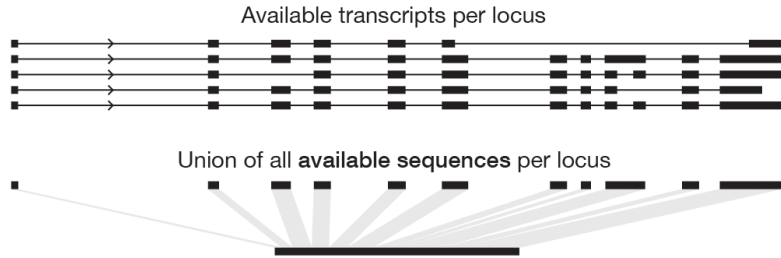
“ Full-length RNA sequences
act as a fundamental crossroad
between genetic makeup &
function! ”



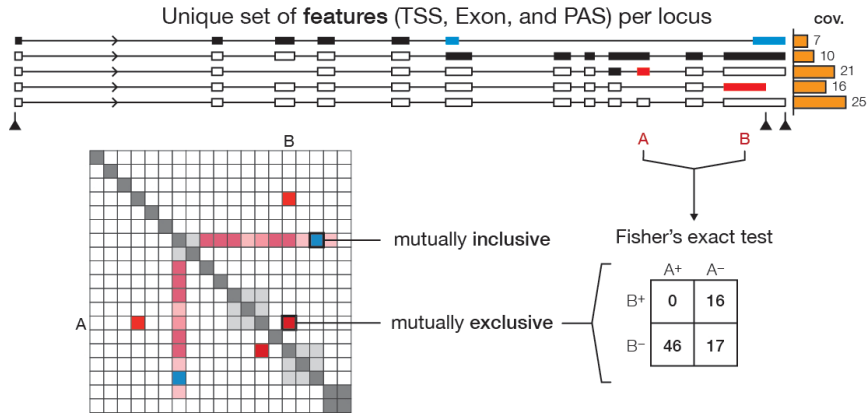
given the space of possible transcript structures,
observation of limited number of transcript
variants suggests the presence of **underlying
mechanisms that tightly control
transcriptional and post-transcriptional
regulation of genes.**



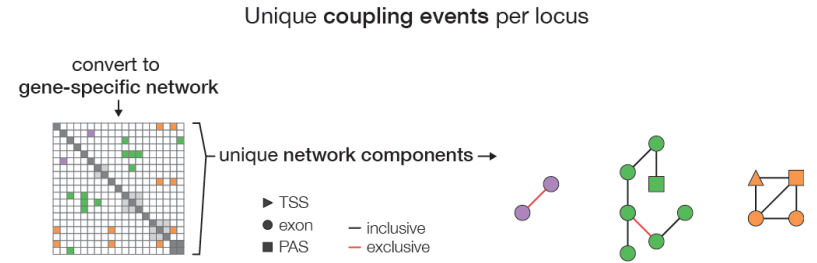
A



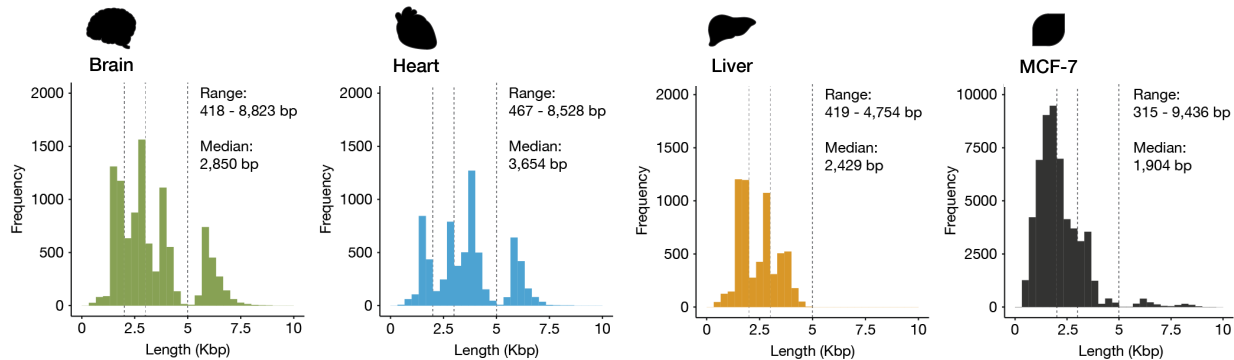
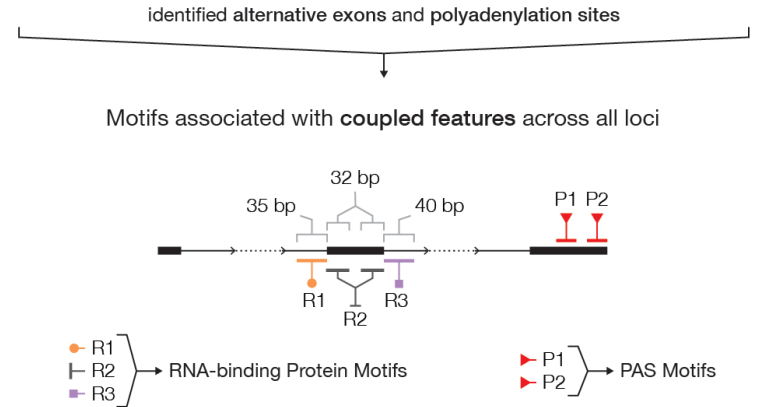
B



C

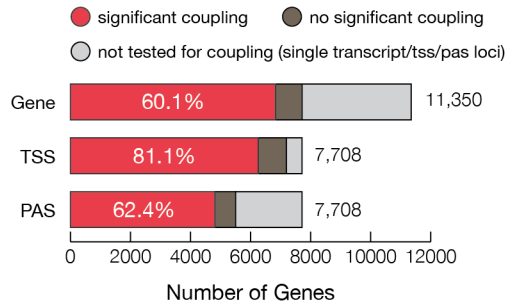


D

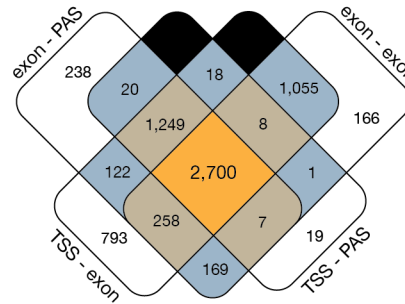


a large number of genes undergo a vigorous preferential selection and coordination during transcription and mRNA processing.

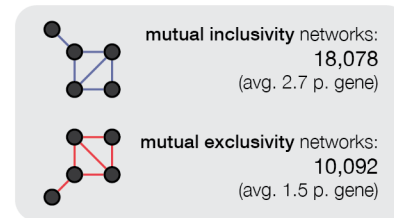
A Genes with Significant Coupling



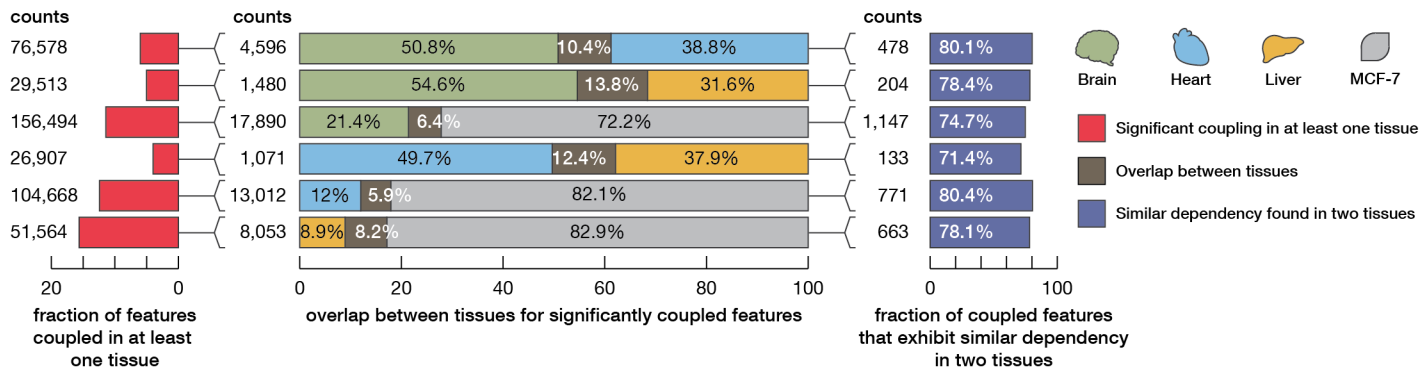
B Coupling per Feature-Pair Type



interdependency networks



Comparison of Coupling between Tissues



Transcript Graph Visualization

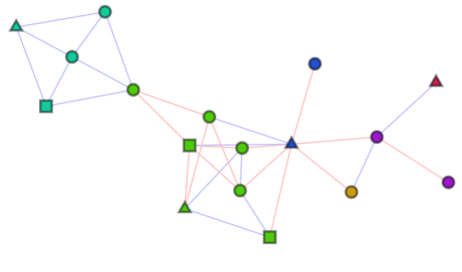
Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

I feel lucky!

PB2016.14533 (MIS12)



Network ▾

+ +/- -

Component ▾

p_value: 0.05

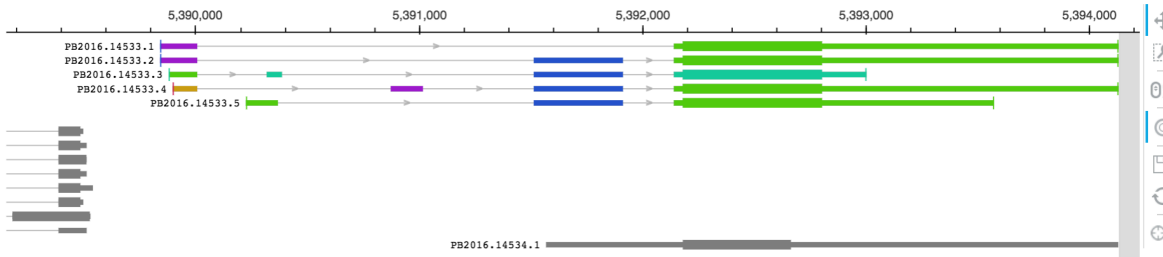
Show Coupling

Split Articulation Points

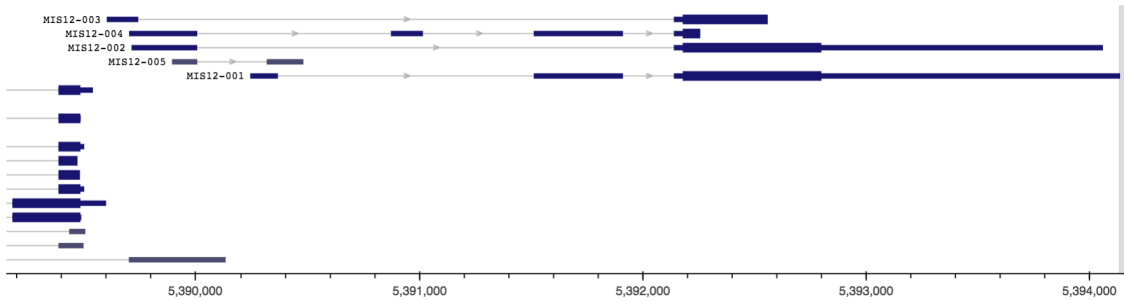
Network (all dependencies)

mcf7plus.2016 Isoseq Transcripts

chr17: 5,389,152 - 5,394,224



Gencode V19 Comprehensive Gene Transcripts



Transcript Graph Visualization

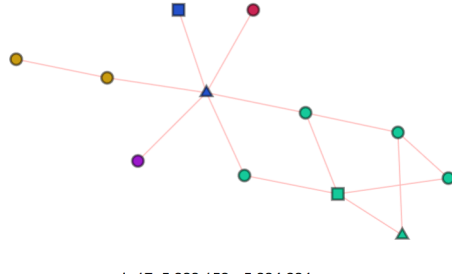
Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

I feel lucky!

PB2016.14533 (MIS12)



Network ▾

+ +/- -

Component ▾

p_value: 0.05

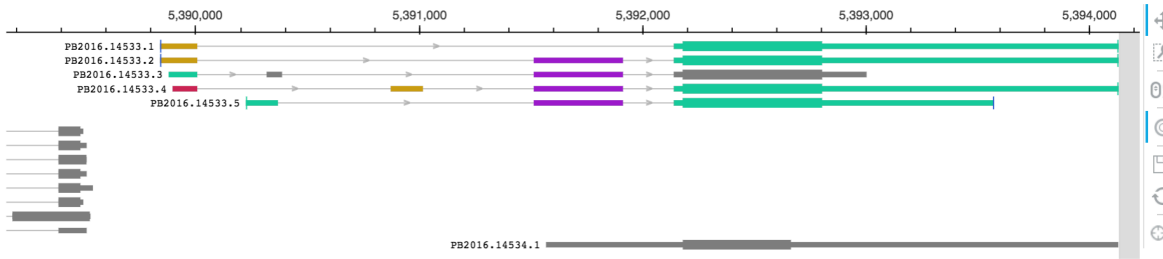
Show Coupling

Split Articulation Points

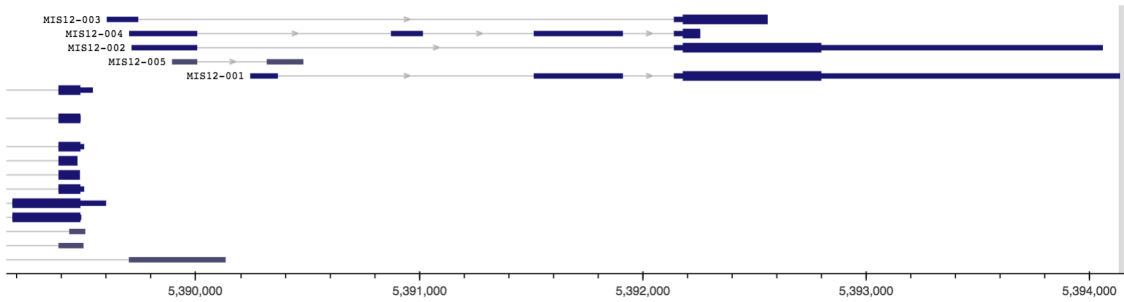
Network (mutual exclusivity)

mcf7plus.2016 Isoseq Transcripts

chr17: 5,389,152 - 5,394,224



Gencode V19 Comprehensive Gene Transcripts



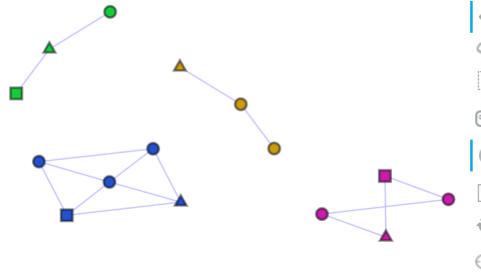
Transcript Graph Visualization

Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

PB2016.14533 (MIS12)



Network ▾

Component ▾

p_value: 0.05

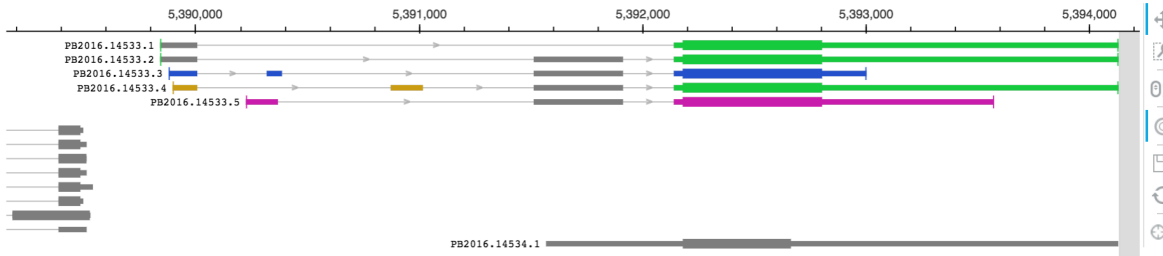
Show Coupling

Split Articulation Points

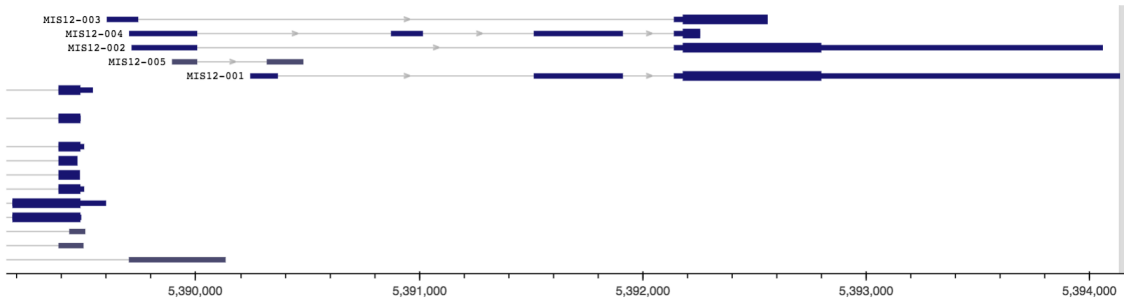
Network (mutual inclusivity)

mcf7plus.2016 Isoseq Transcripts

chr17: 5,389,152 - 5,394,224



Genecode V19 Comprehensive Gene Transcripts



Transcript Graph Visualization

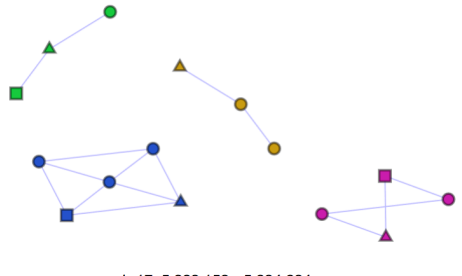
Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

I feel lucky!

PB2016.14533 (MIS12)



Network ▾

+ +/- -

Component ▾

p_value: 0.05

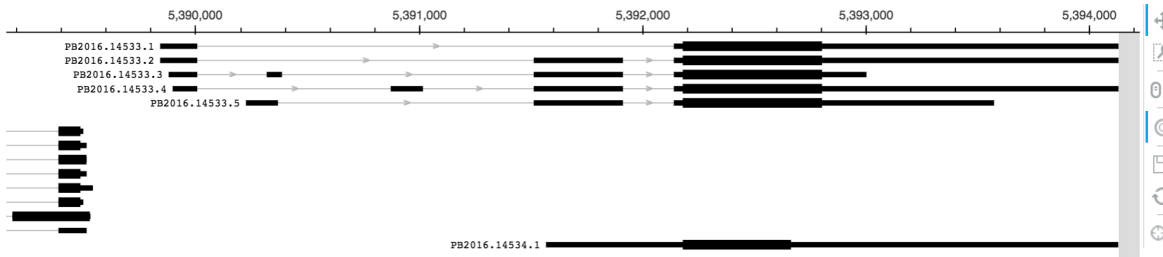
Show Coupling

Split Articulation Points

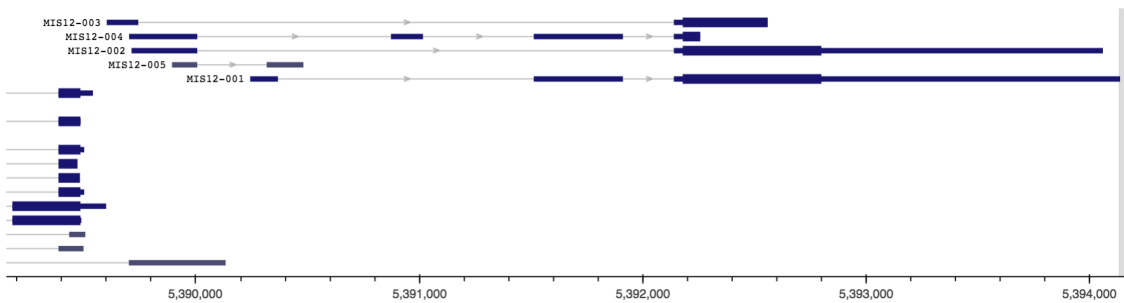
Hide colouring based on coupling network

mcf7plus.2016 Isoseq Transcripts

chr17: 5,389,152 - 5,394,224



Gencode V19 Comprehensive Gene Transcripts



Transcript Graph Visualization

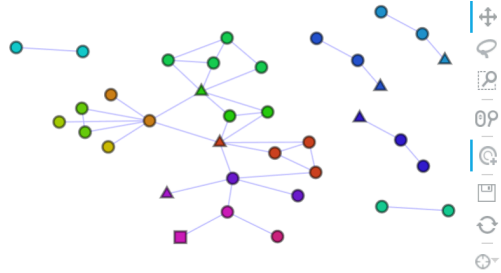
Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

I feel lucky!

PB2016.10041 (EIF4G2)



Network ▾

+ +/- -

Component ▾

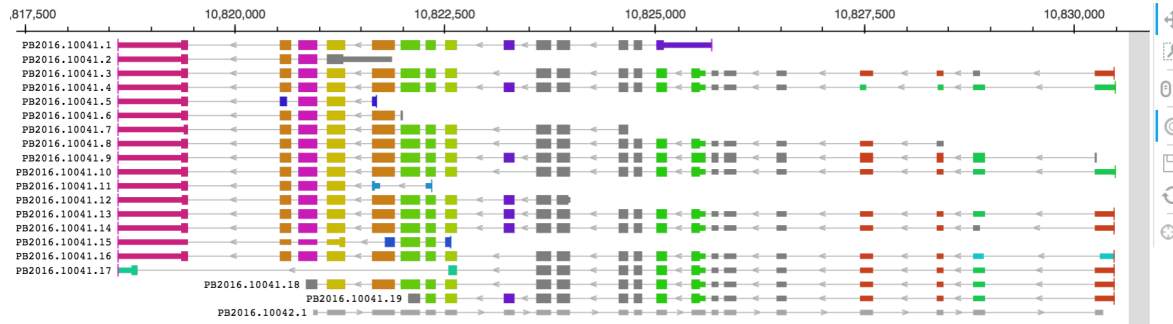
p_value: 0.05

Show Coupling

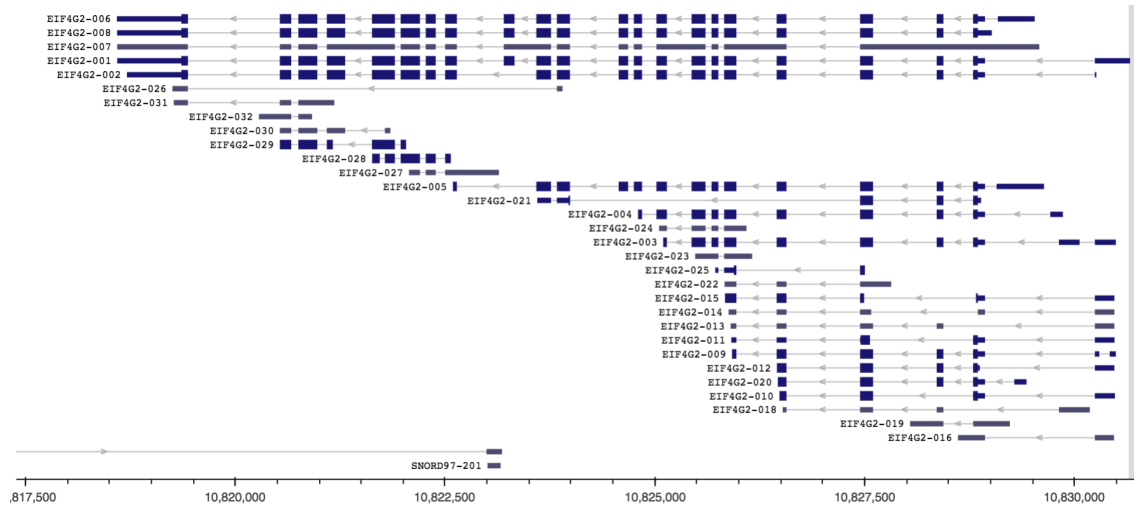
Split Articulation Points

mcf7plus.2016 Isoseq Transcripts

chr11: 10,817,391 - 10,830,898



Gencode V19 Comprehensive Gene Transcripts



Transcript Graph Visualization

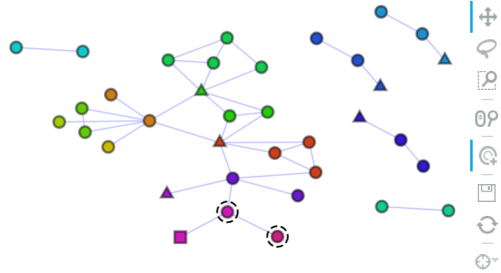
Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:

I feel lucky!

PB2016.10041 (EIF4G2)



Network ▾

+ +/- -

Component ▾

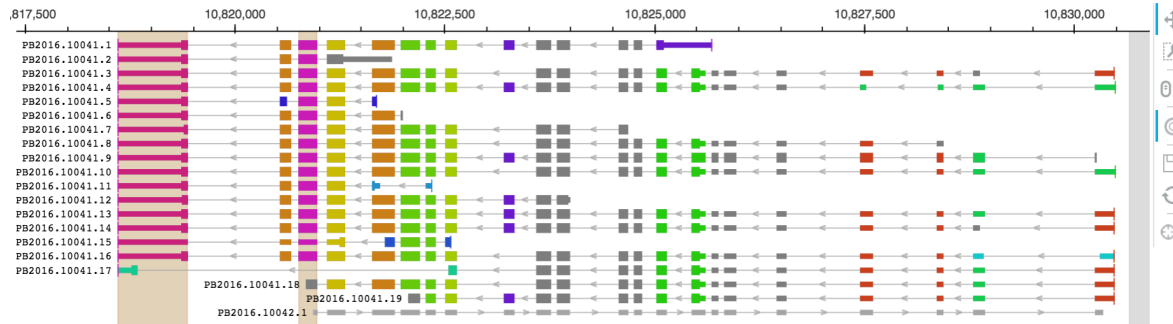
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Show Coupling

Split Articulation Points

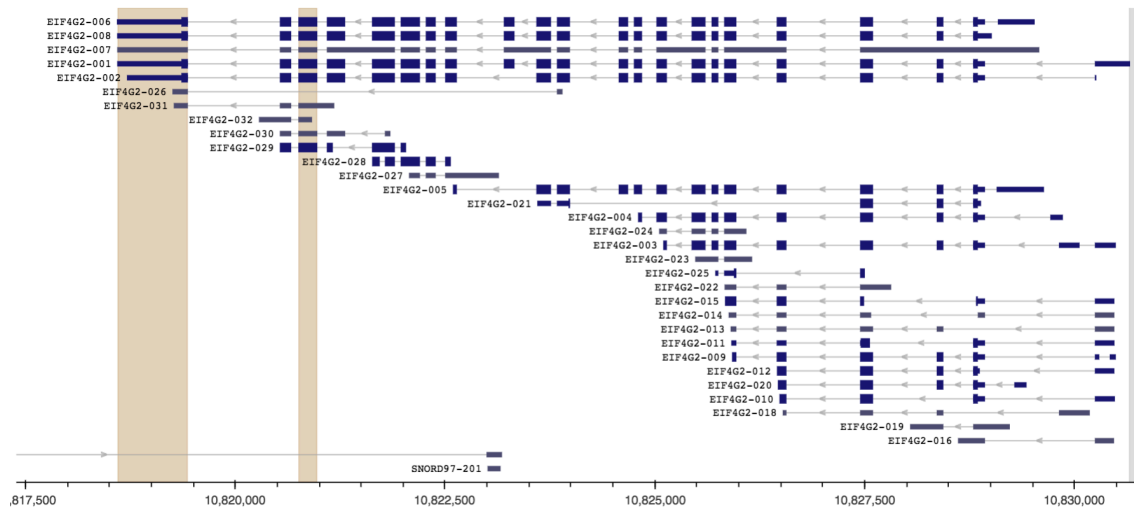
mcf7plus.2016 Isoseq Transcripts

chr11: 10,817,391 - 10,830,898



Examining complex networks

Gencode V19 Comprehensive Gene Transcripts

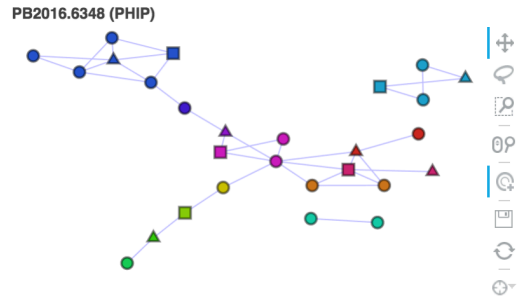


Transcript Graph Visualization

Dataset: mcf7plus.2016 ▾

Locus search:

Gene search:



Network ▾

+ +/- -

Component ▾

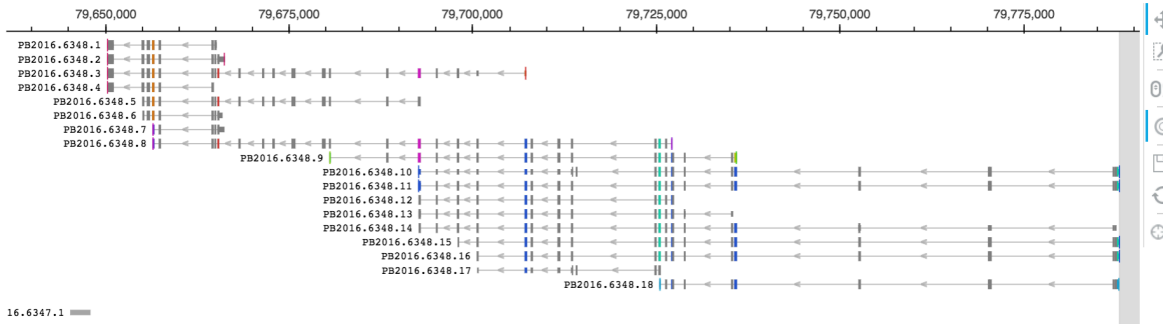
p_value: 0.05

Show Coupling

Split Articulation Points

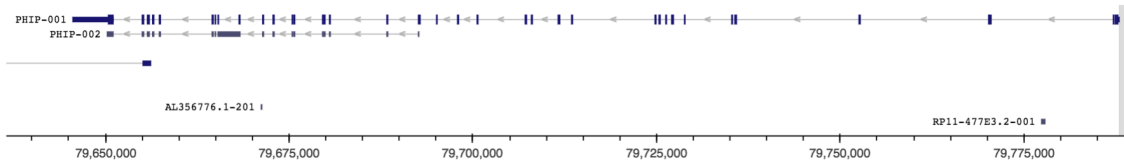
mcf7plus.2016 Isoseq Transcripts

chr6: 79,636,522 - 79,790,761



Underestimation of alternative splicing, reflected by Gencode annotation

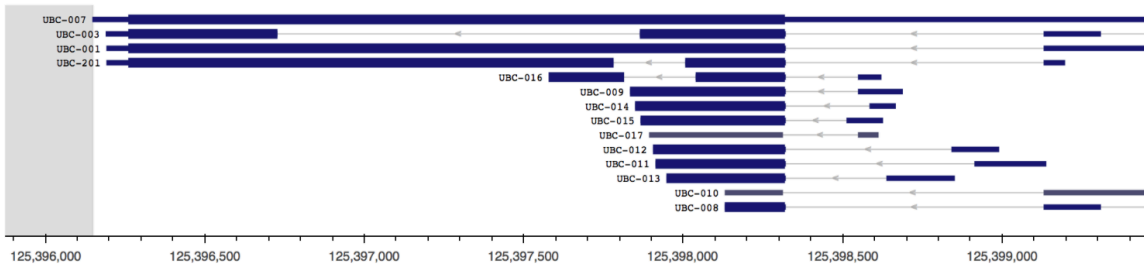
Gencode V19 Comprehensive Gene Transcripts

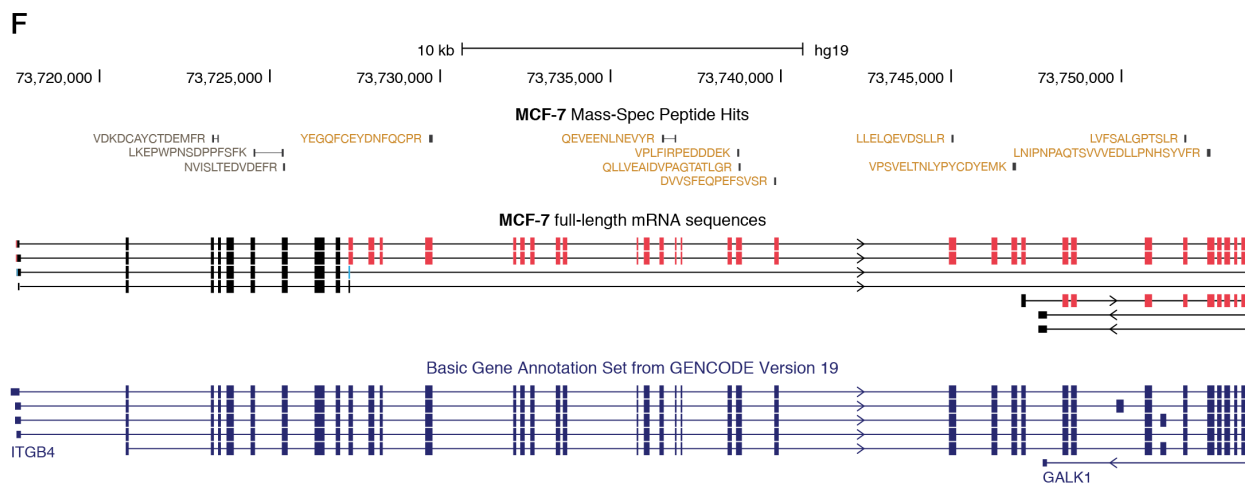
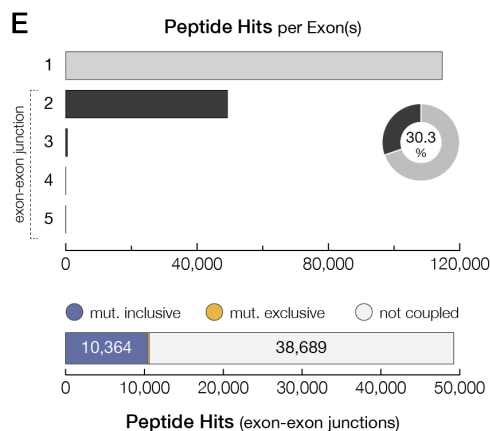
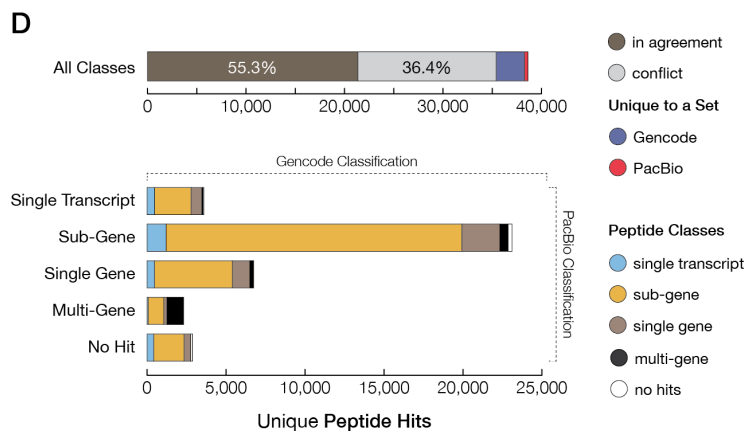
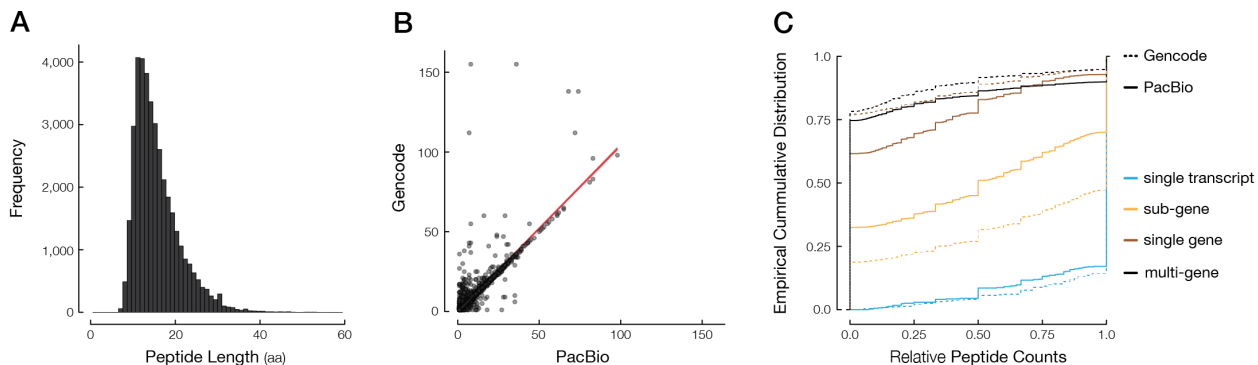


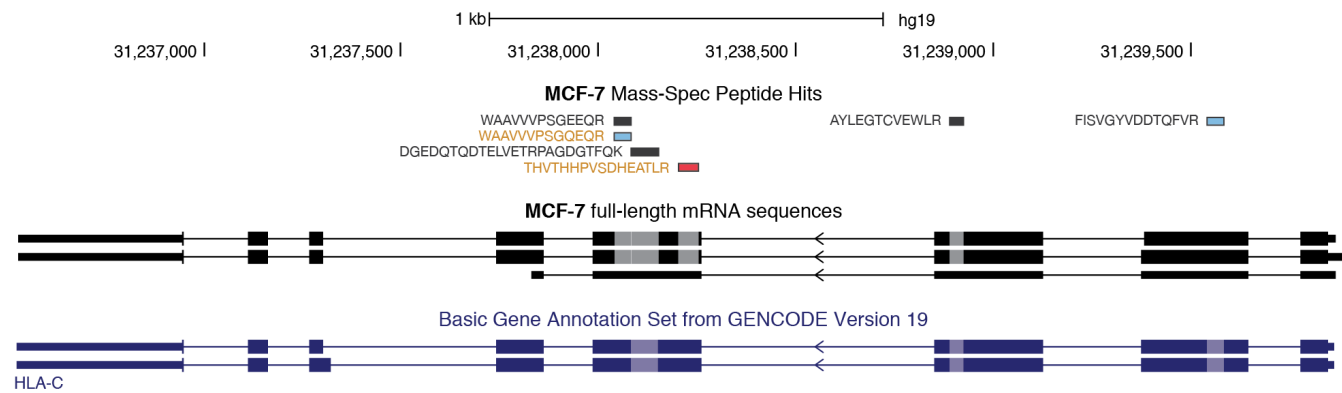
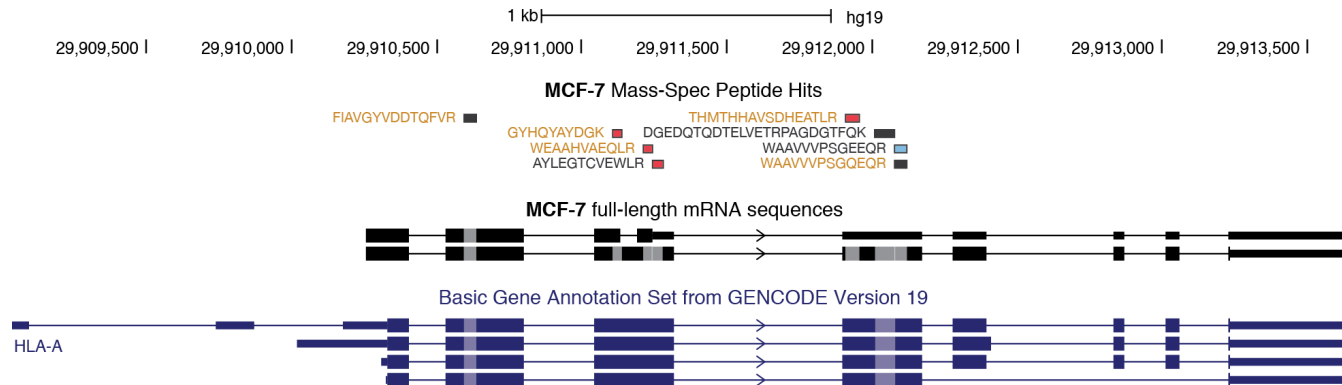


Resolution of complex RNA splicing patterns and their functional consequence

Gencode V19 Comprehensive Gene Transcripts

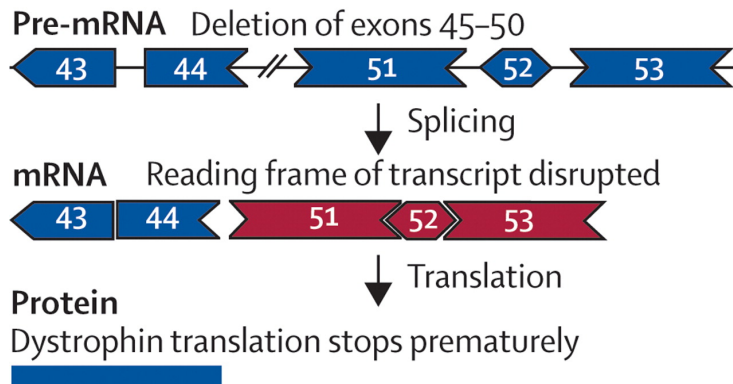




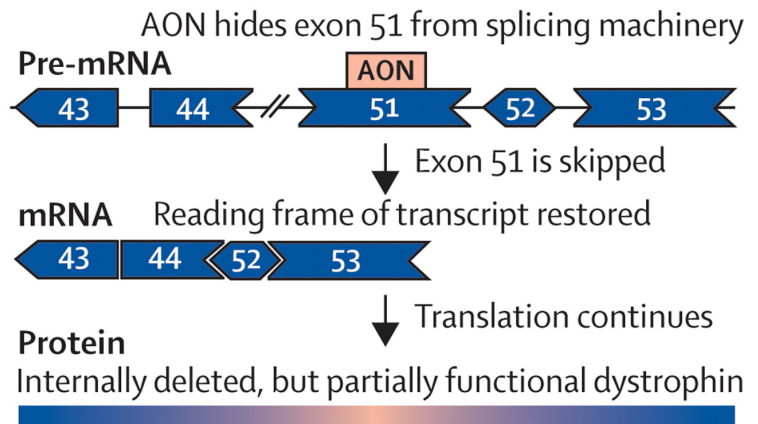


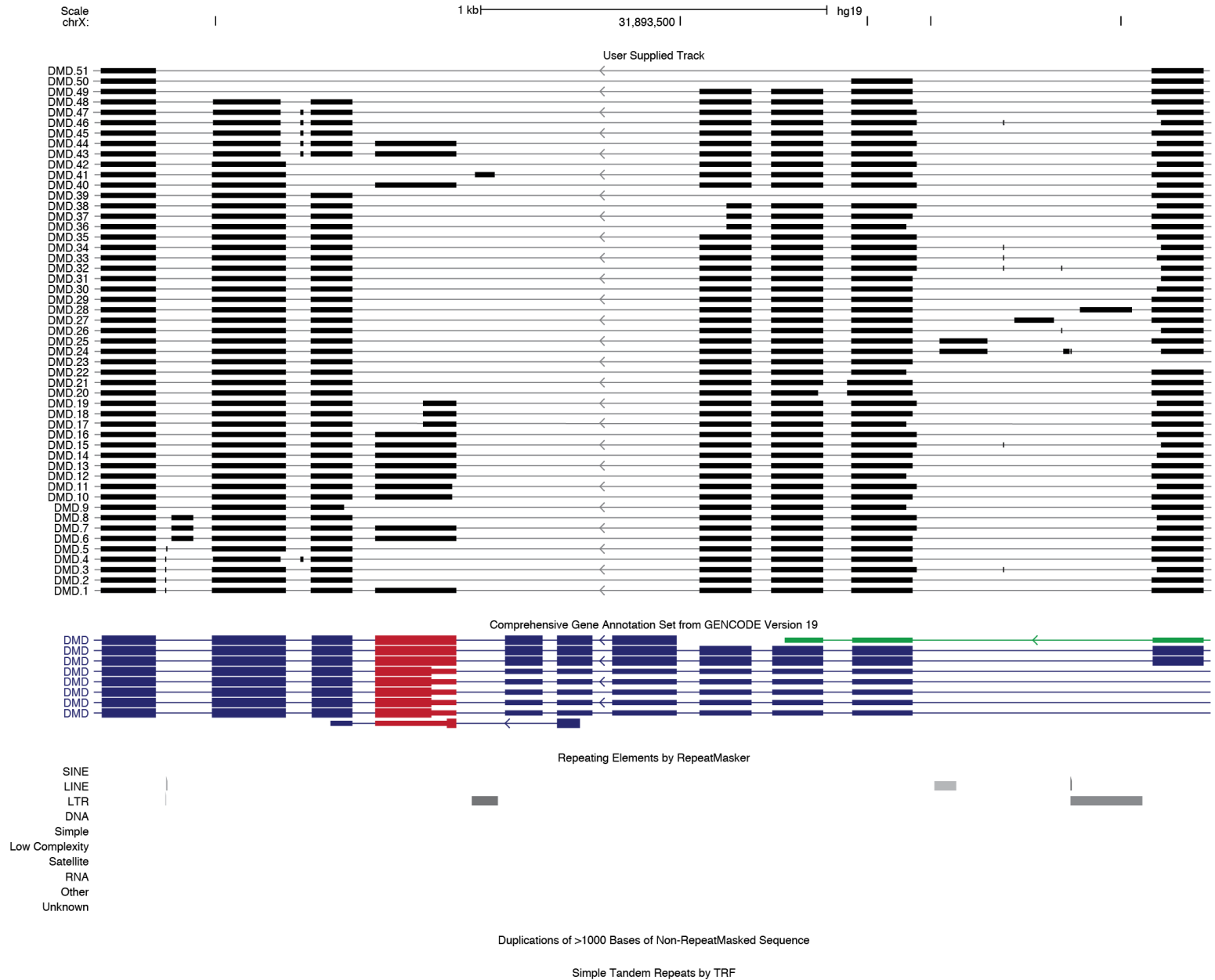
the value of **resolving full-length mRNA** in **translational medicine**: assessing the efficacy and the presence of adverse events.

Duchenne muscular dystrophy



Exon skipping to reframe transcripts





THANK YOU FOR YOUR ATTENTION!

I would welcome any
questions or suggestions
you might have!

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