An overview of the RNUopathies

Adam Jackson

University of Manchester

Manchester ESHG Syndromology and Dysmorphology Course 2026

MANCHESTER 1824 The University of Manchester
NHS Manchester University NHS Foundation Trust
MCGM
Manchester Rare Conditions Centre
Rare Disease Research UK. Epigenomics of Rare Disorders - EpiGenRare
NIHR | Manchester Biomedical Research Centre

‘RNU’ genes

Small nuclear RNAs (snRNA)
<200bp length
~2000 annotations in human genome

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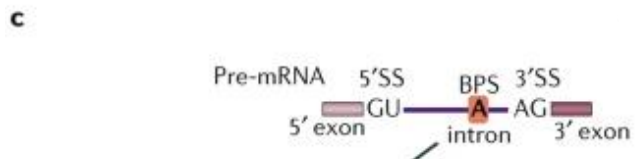
RN	RNA
U	U-rich (forms the SM binding site – AUUUUUG-)
4-2	4 is the type of specific RNA molecular (U4) and -2 is the genomic locus

snRNAs coordinate splicing



Nature Reviews | Molecular Cell Biology

Shi. Nat Rev Mol Cell Biol. 2017.

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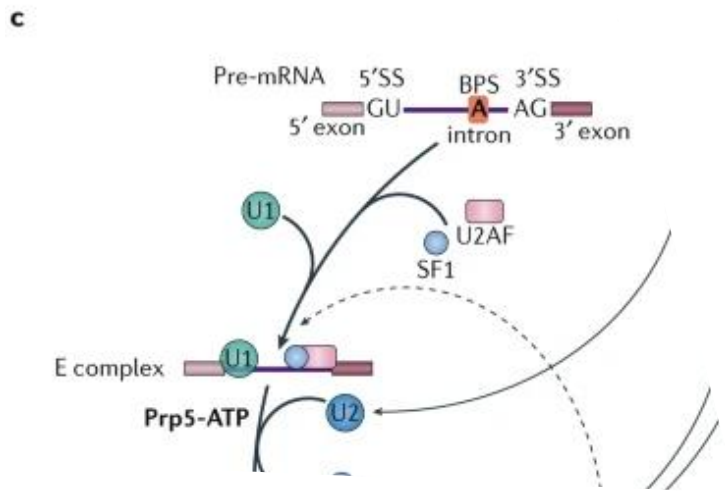

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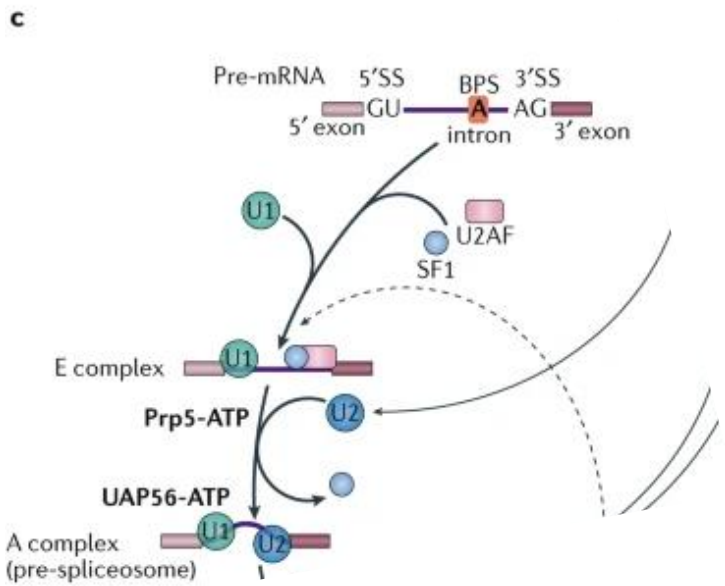

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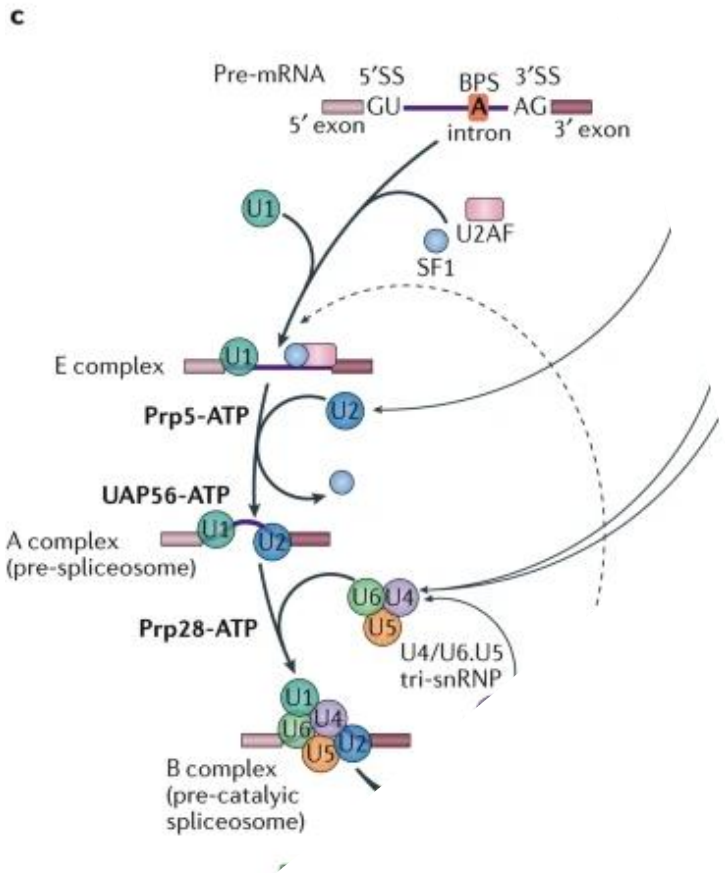

Nature Reviews | Molecular Cell Biology

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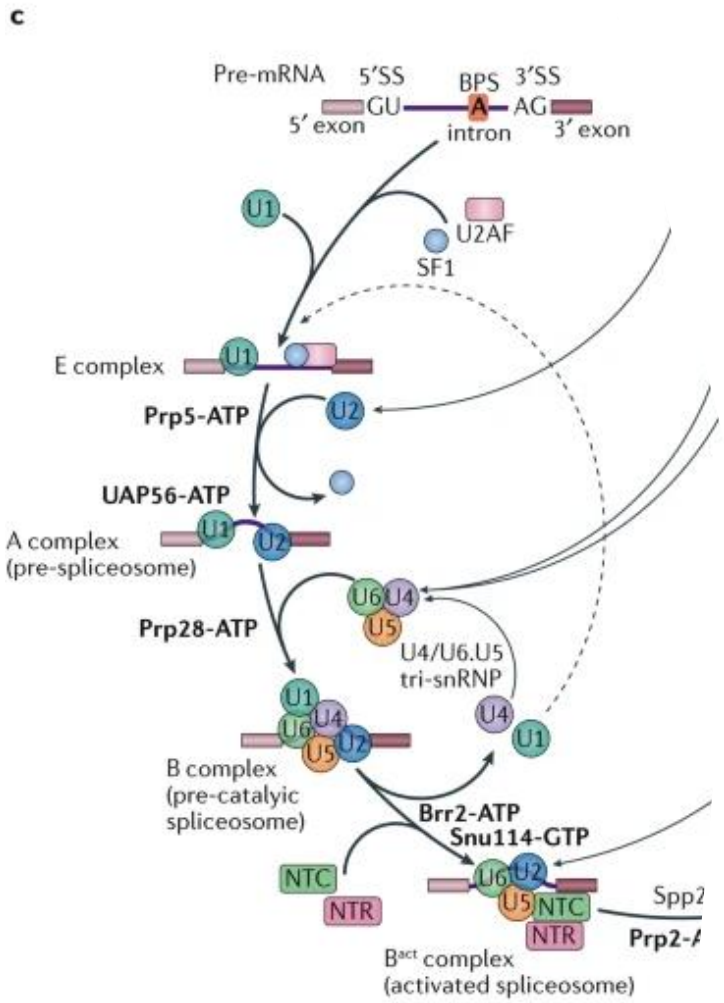

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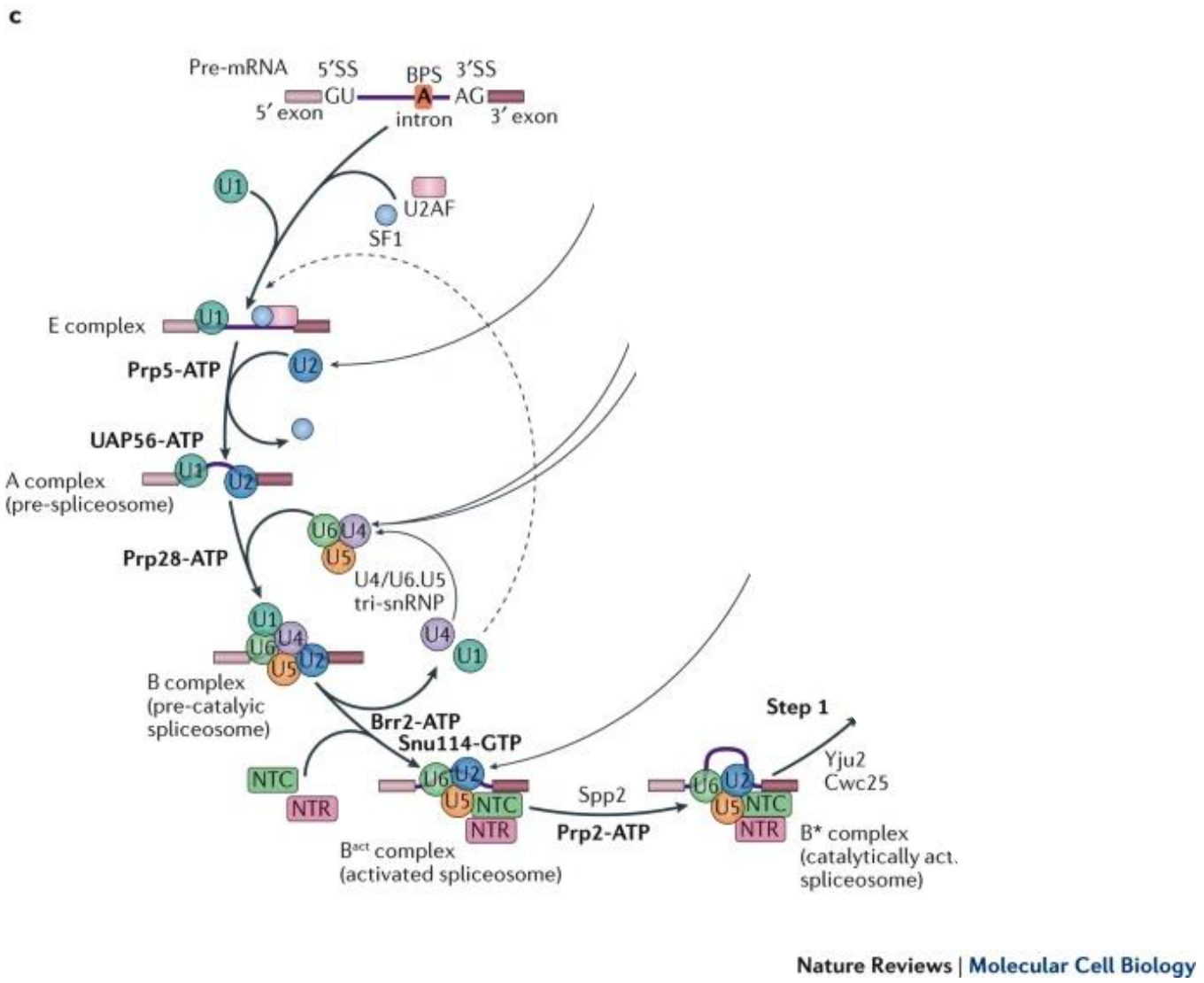

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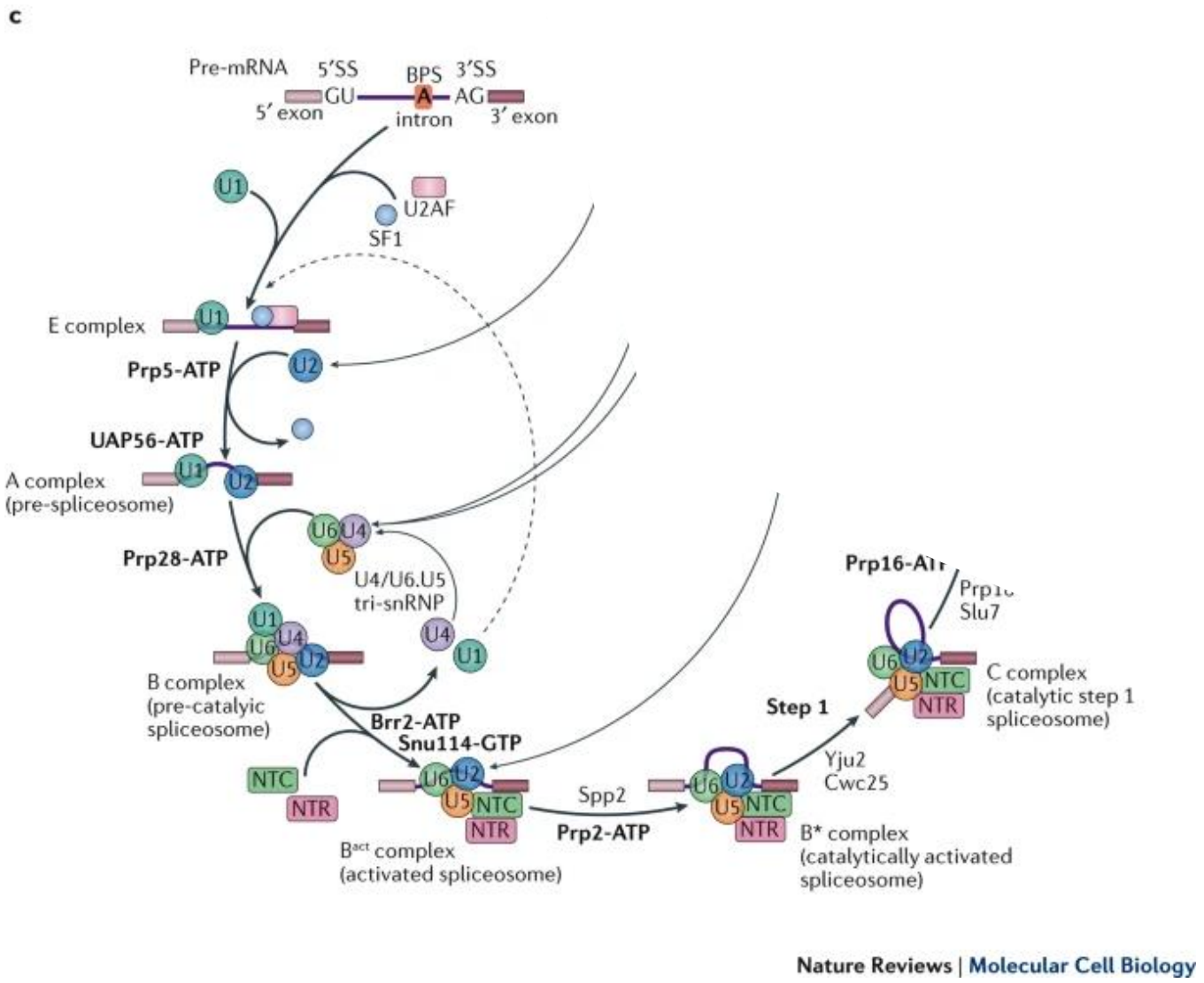

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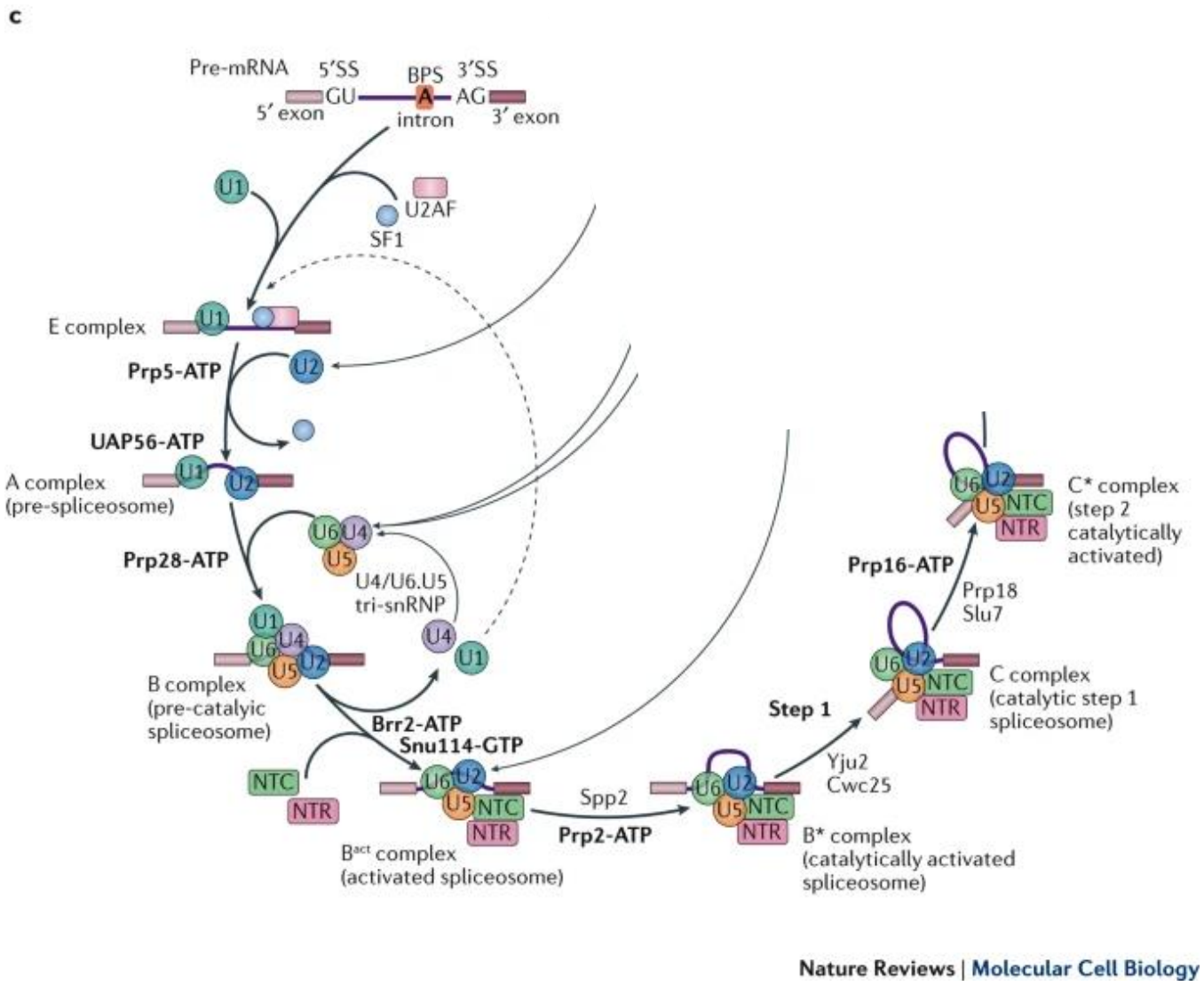

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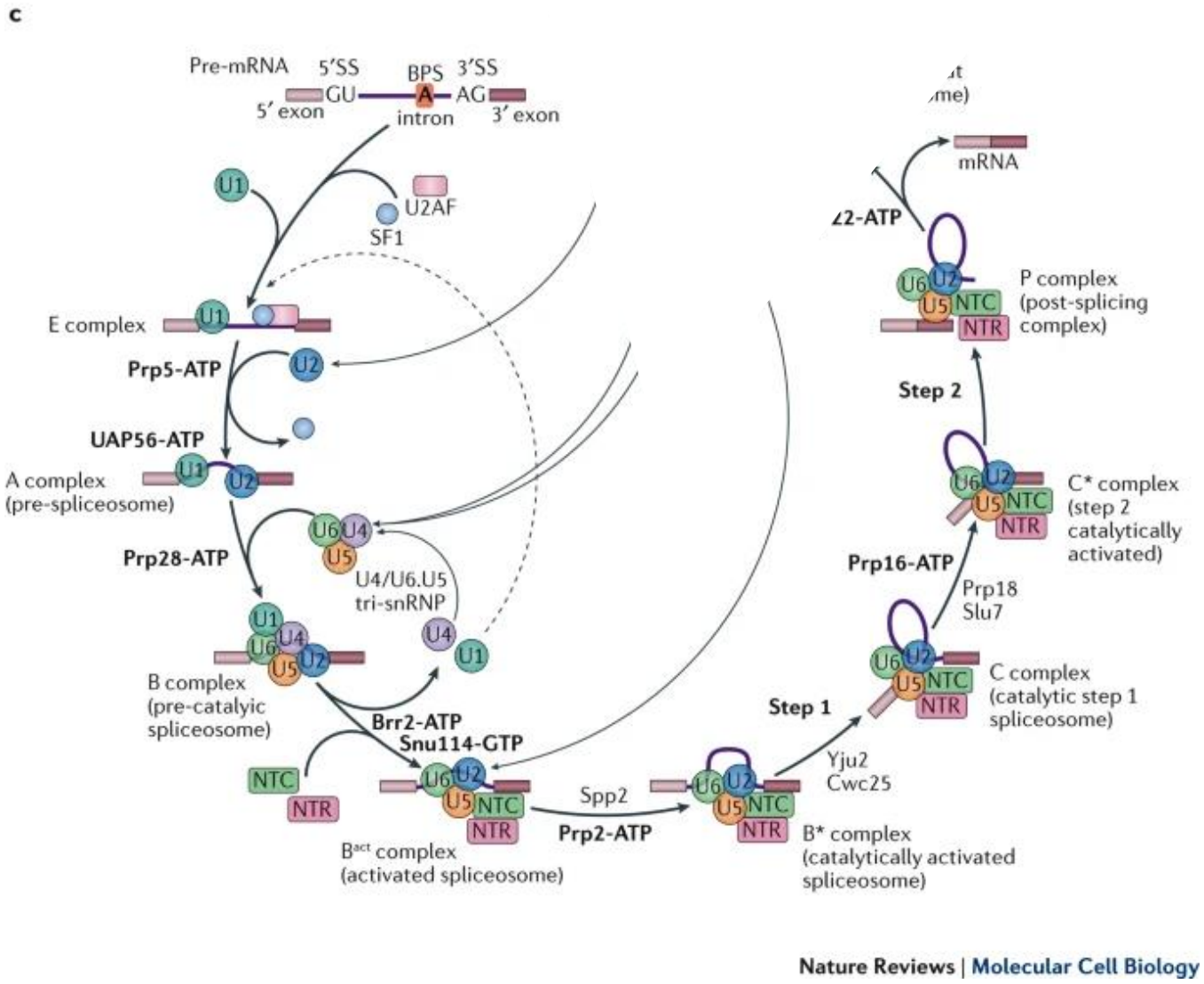

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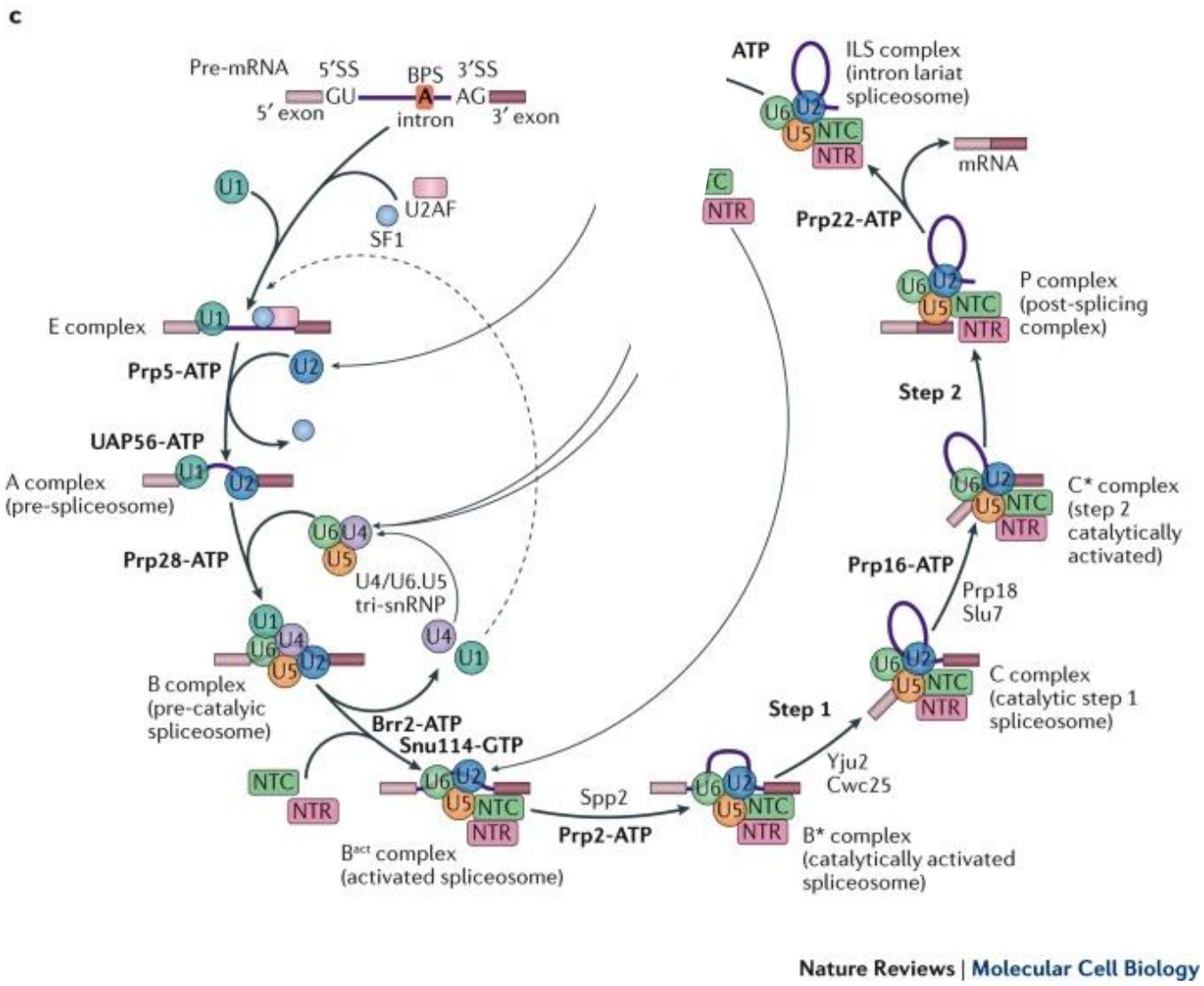

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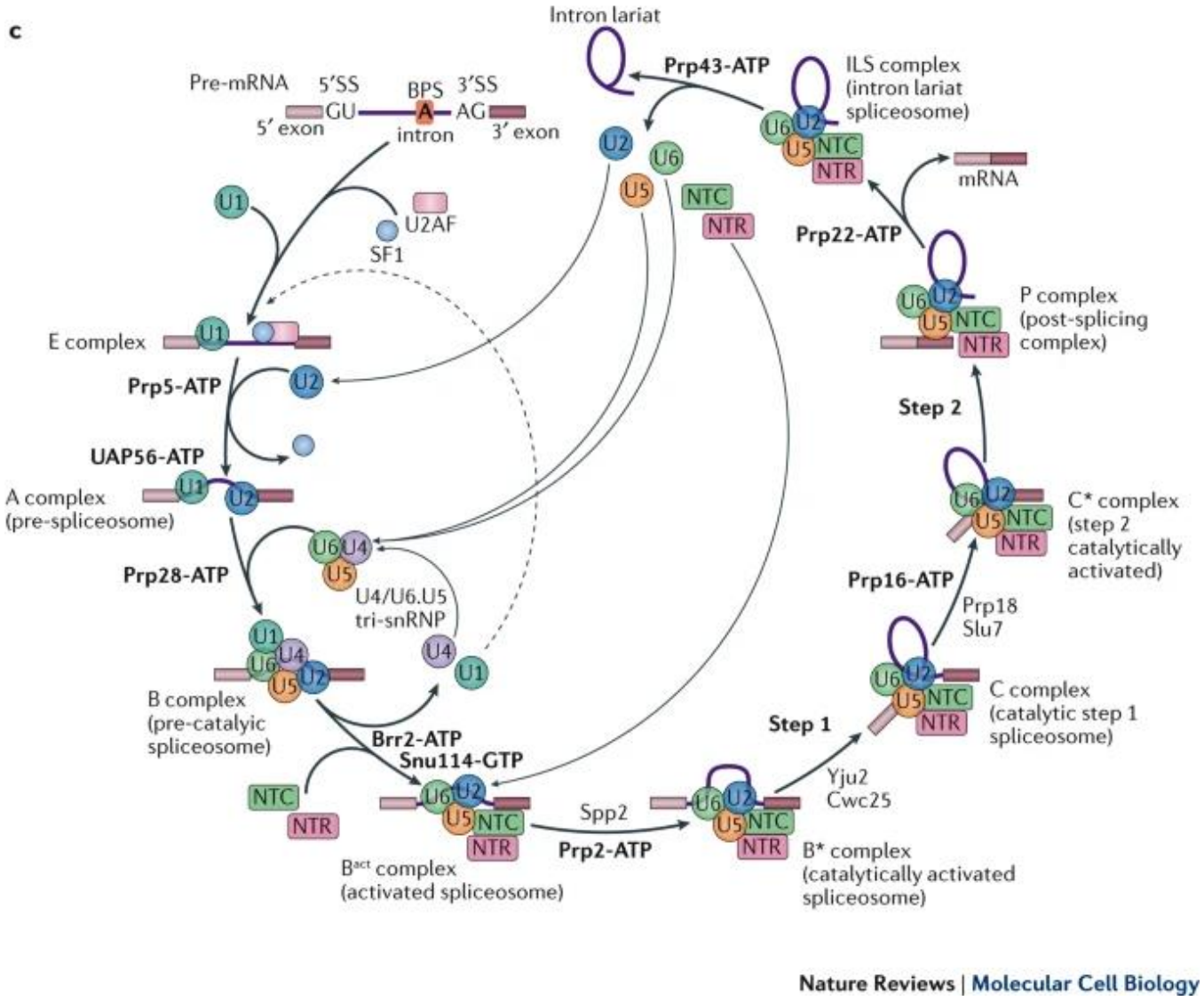
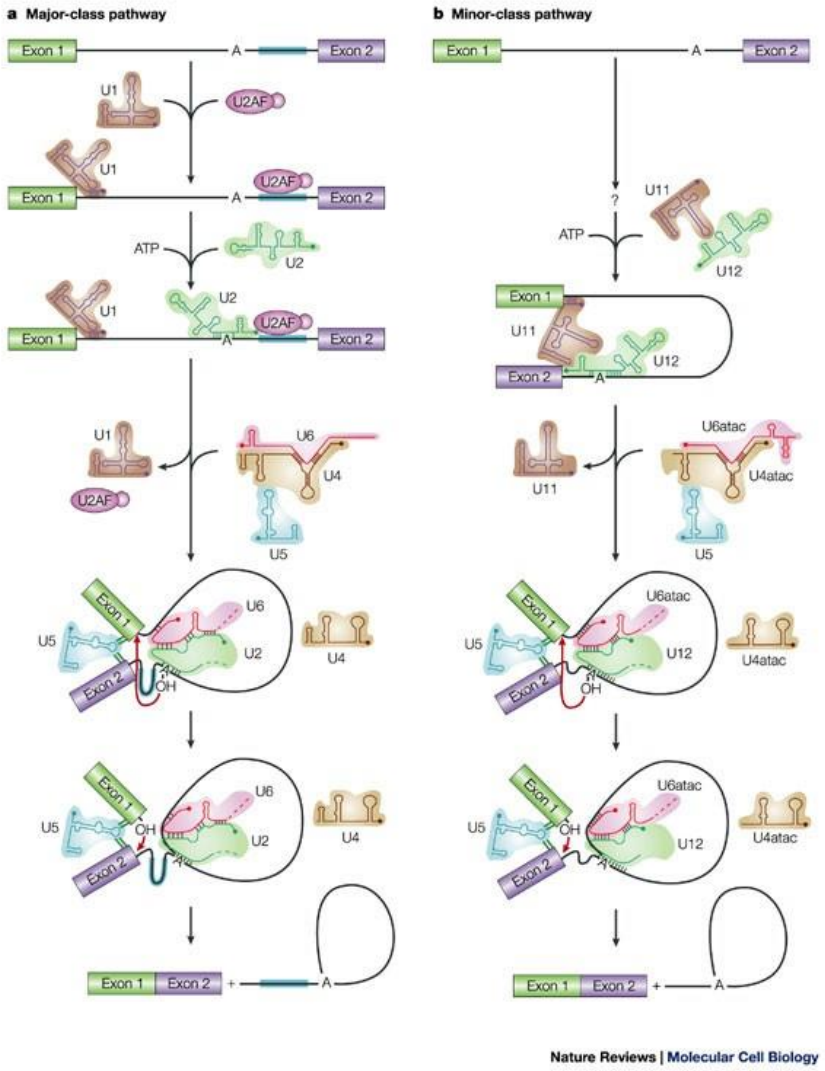
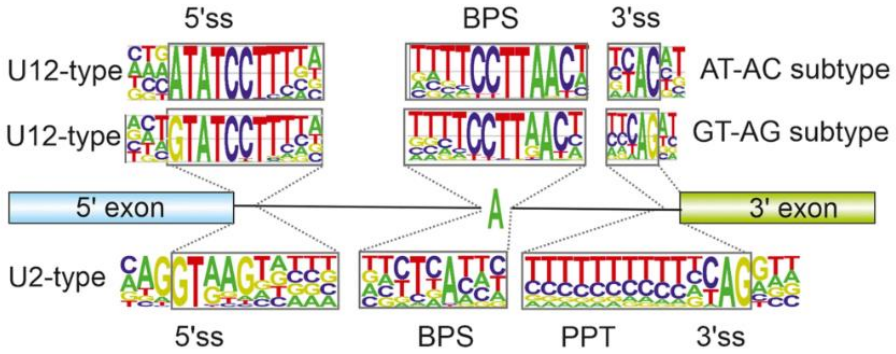


Shi. Nat Rev Mol Cell Biol. 2017.

Splicing comes in two flavors in eukaryotes



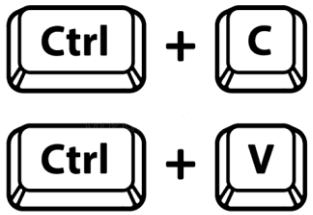


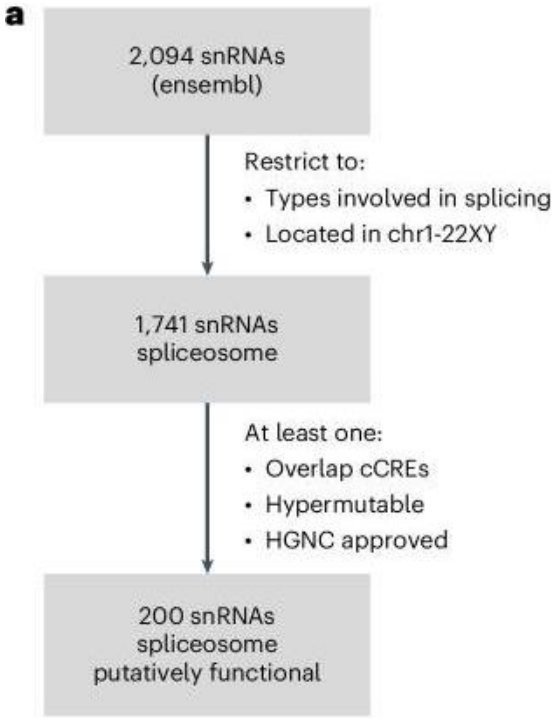


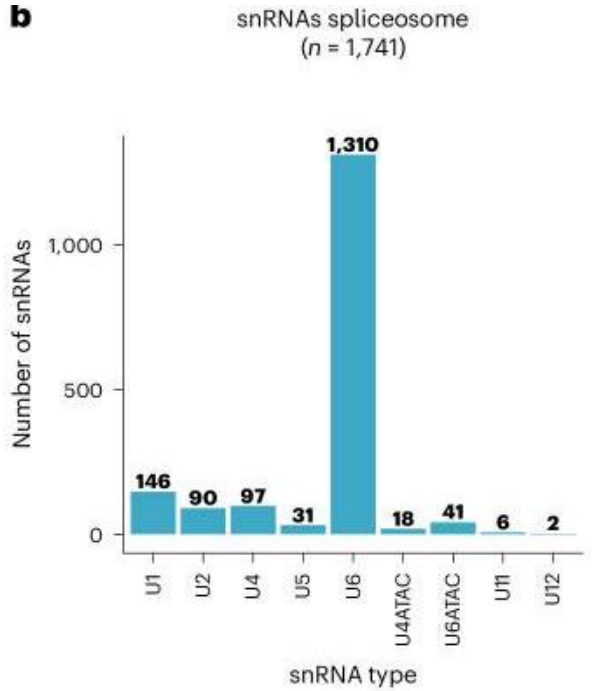
	Major	Minor
Acceptor recognition	U1	U11
Branchpoint recognition	U2	U12
Spliceosome activation	U4	U4ATAC
Exon apposition	U5	U5
Catalytic acceptor recognition	U6	U6ATAC

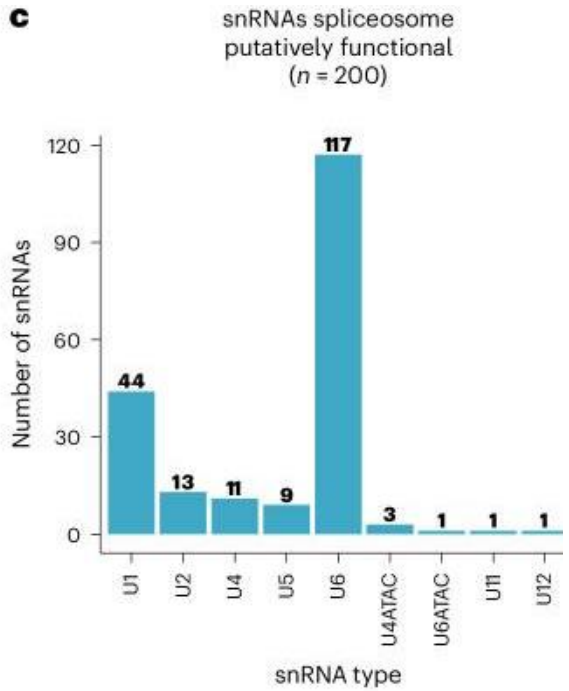
Patel and Steitz. Nat Rev Genet. 2003. Akinyi and Frilander. Front Genet. 2021.

snRNA genes multiple by retrotransposition





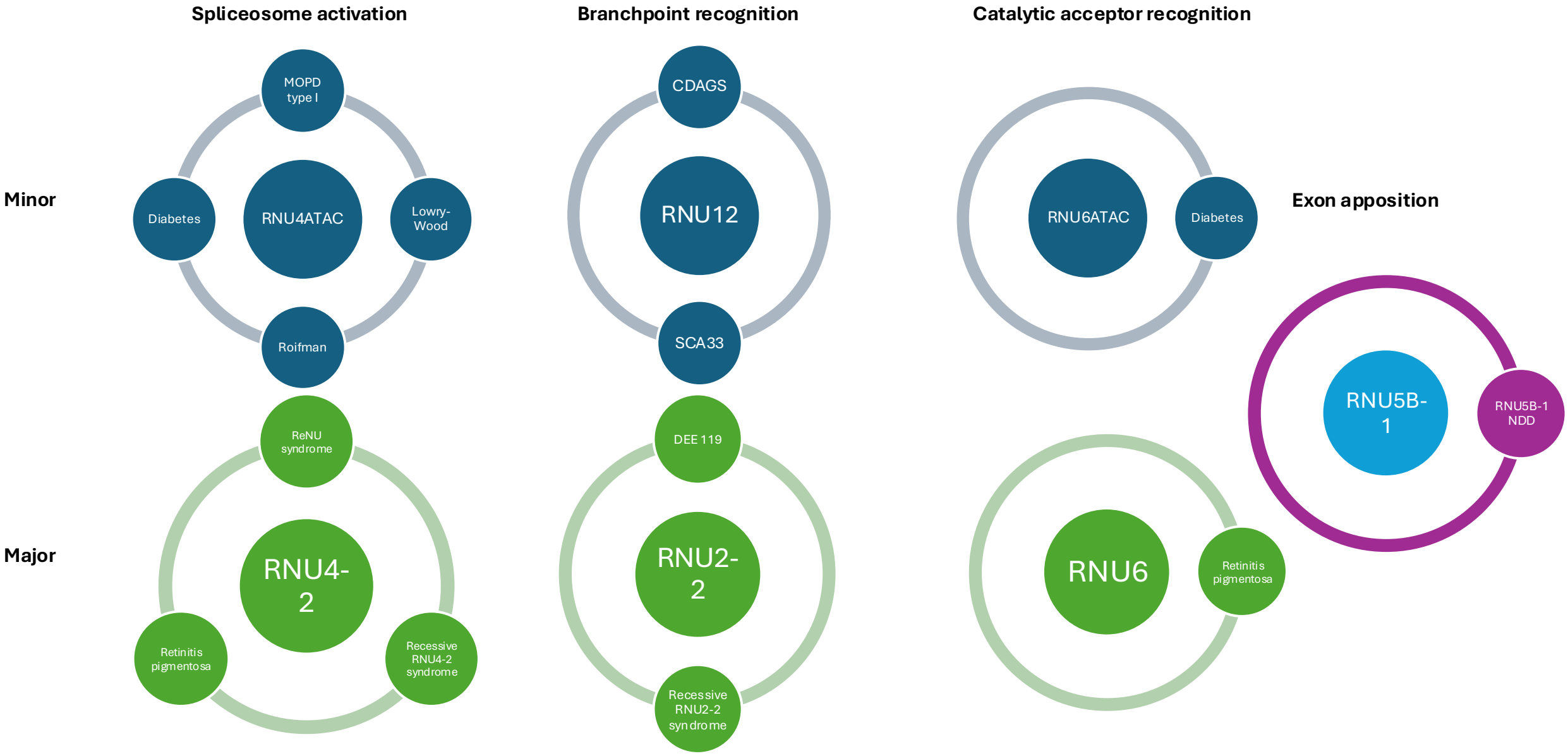




Could variants in snRNAs be disease-causing?

Leitao et al. Nat Genet. 2026

Variants in the major paralogs of snRNAs can cause disease



RNU4ATAC: three recessive clinical phenotypes (128bp)

Gene-Phenotype Relationships

Location	Phenotype View Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
2q14.2	Lowry-Wood syndrome	226960	AR	3
	Microcephalic osteodysplastic primordial dwarfism, type I	210710	AR	3
	Roifman syndrome	616651	AR	3

MOPDI: microcephaly, IUGR, skeletal dysplasia



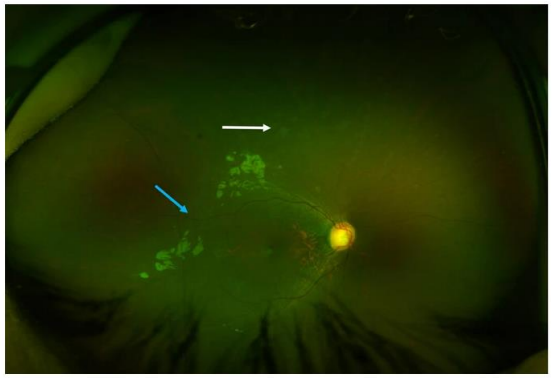
Kroigard et al. Clin Dysmorphology 2016

LWS: multiple epiphyseal dysplasia, microcephaly



Farach et al. AJMG. 2019

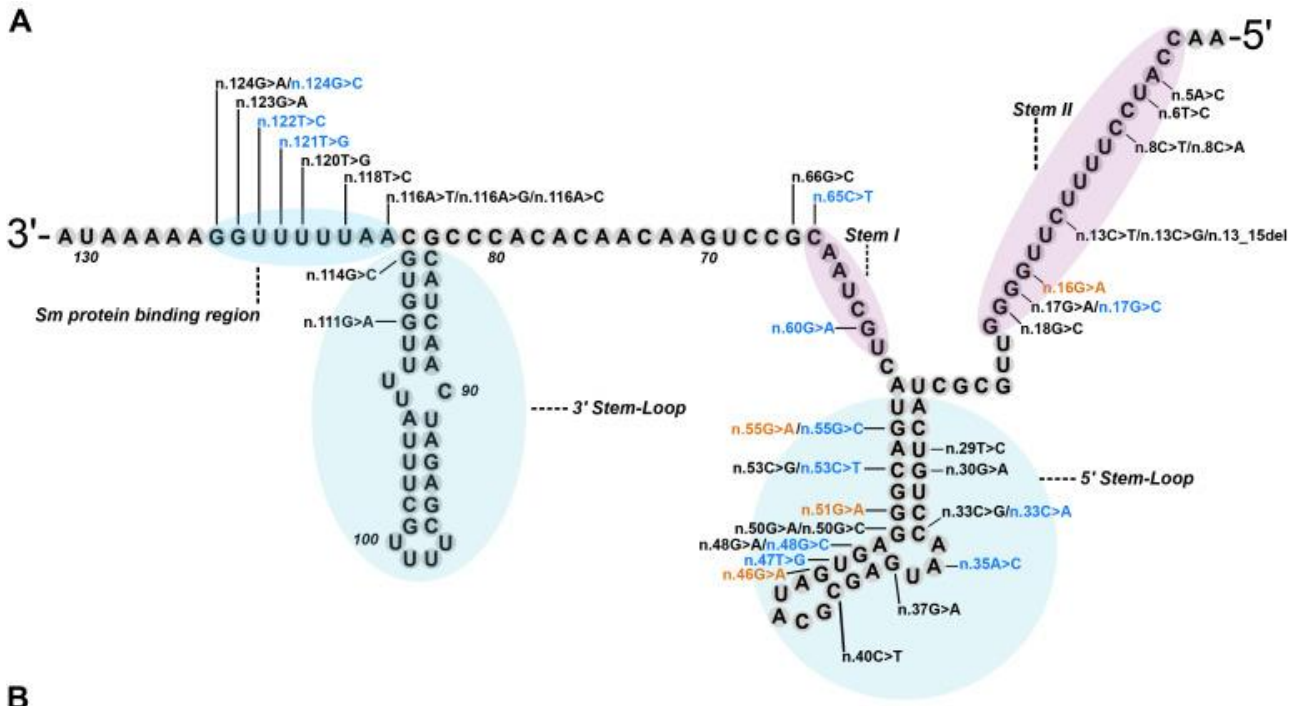
Roifman syndrome: spondyloepiphyseal dysplasia, retinal degeneration and immunodeficiency

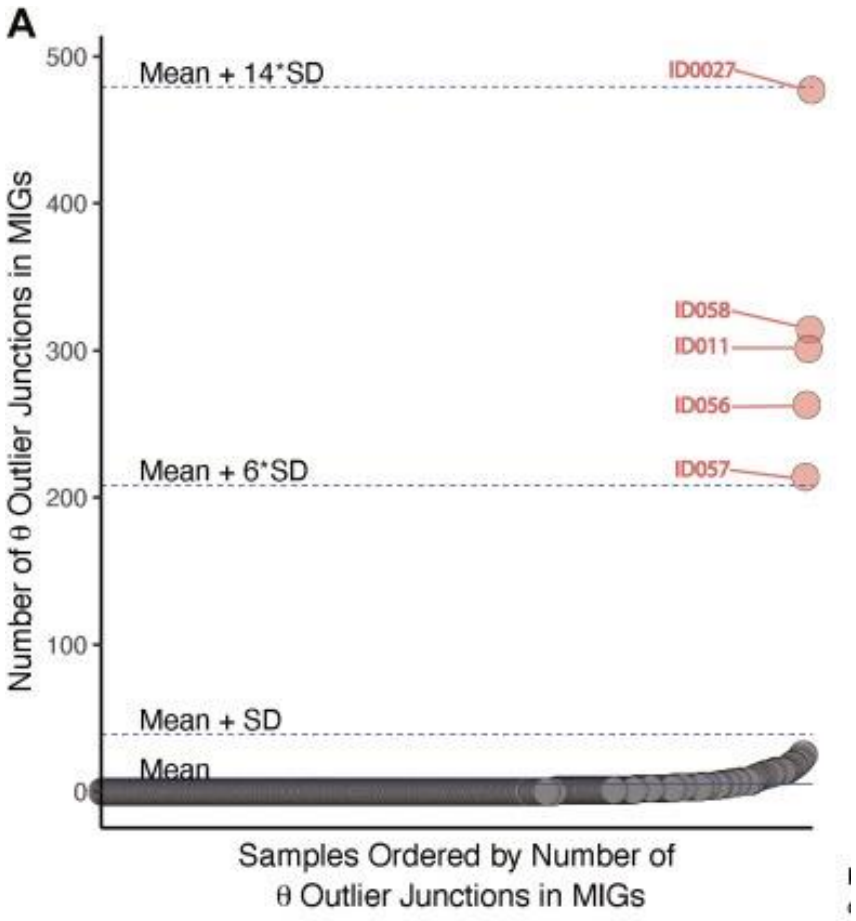


Schejter et al. NPJ Genomic Medicine. 2017

How can three phenotypes be causes by biallelic variants in the same gene?

RNU4ATACopathy spectrum and minor intron retention

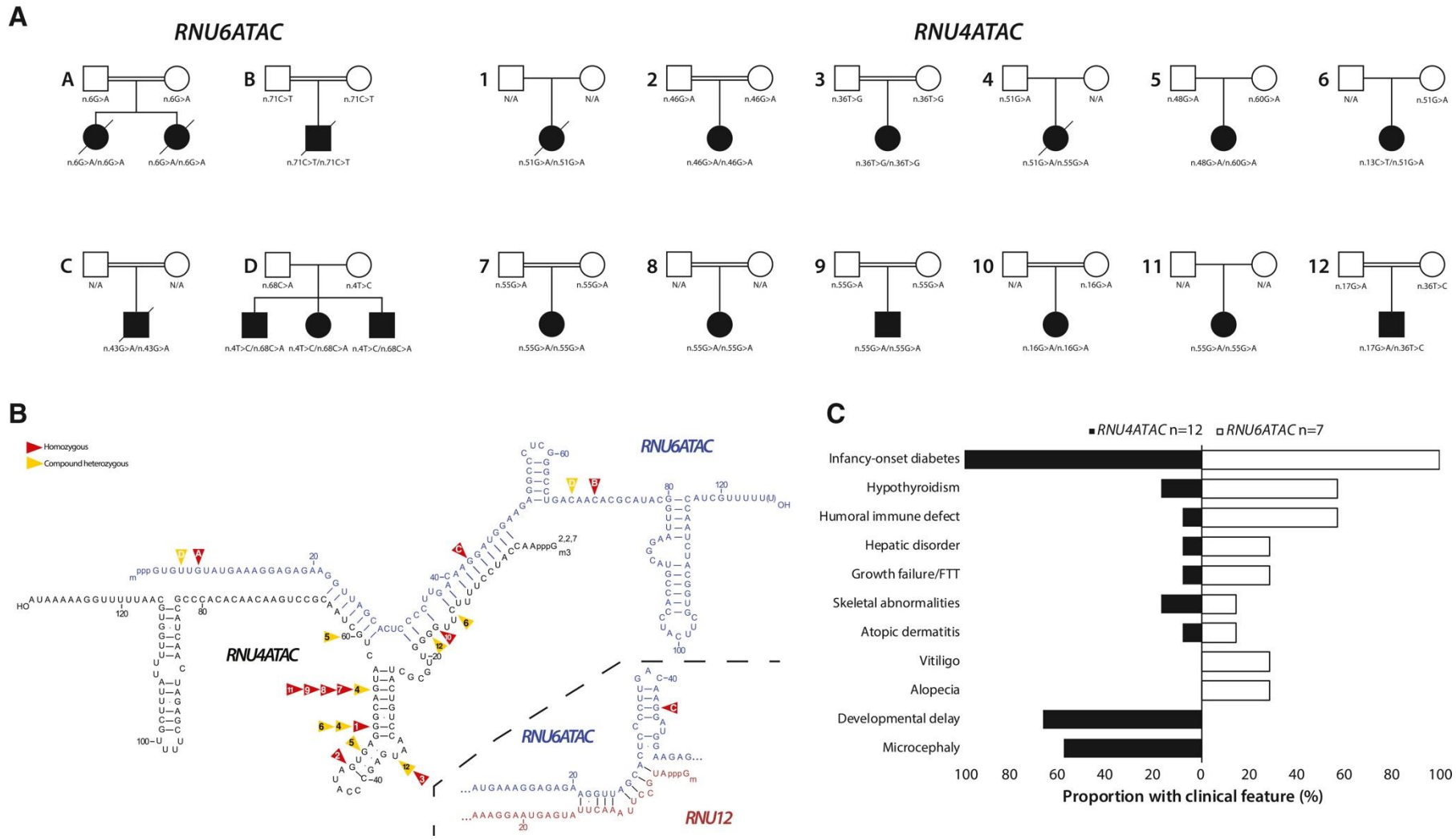




How broad can the spectrum be?

Matalon et al. Genet Medicine. 2026.

Monogenic immune diabetes and the minor spliceosome



A few patients with diabetes alone!

Johnson et al. AJHG. 2026

RNU12: two recessive clinical phenotypes (150bp)

Gene-Phenotype Relationships

Location	Phenotype (View Clinical Synopses)	Phenotype MIM number	Inheritance	Phenotype mapping key
22q13.2	?Spinocerebellar ataxia, autosomal recessive 33	620208	AR	3
	CDAGS syndrome	603116	AR	3

CDAGS: craniosynostosis, delayed closure of fontanelle, anal anomalies, GU malformations, skin manifestations

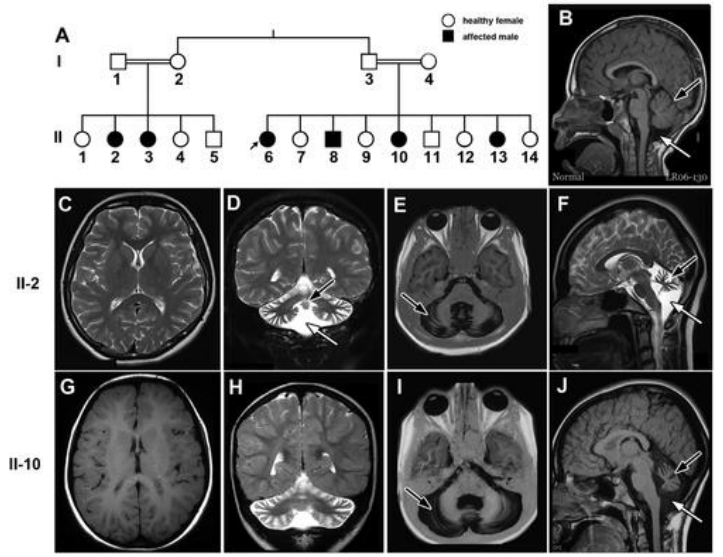


Xing et al. Human Mutation 2021

Both affect splicing

MIR demonstrated in SCA33 only

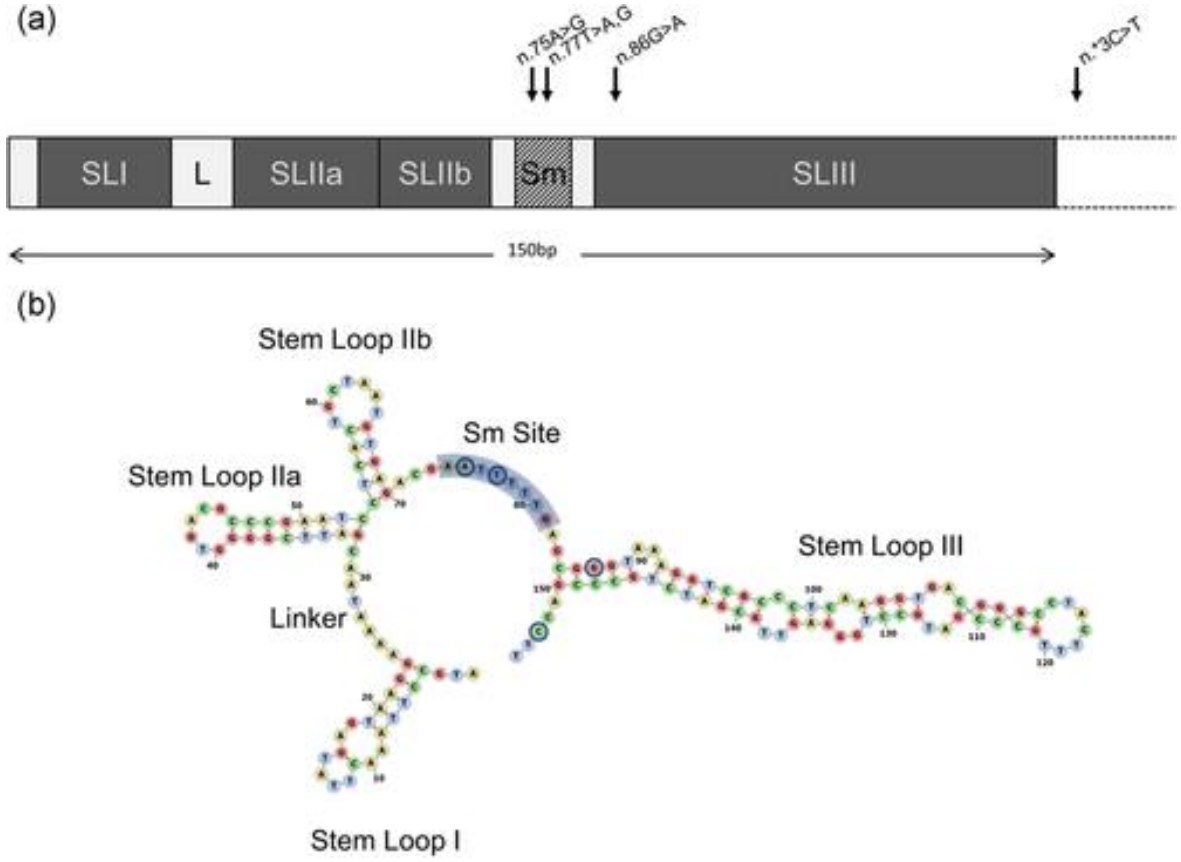
SCA33: cerebellar ataxia with learning difficulties



Elsaid et al. Annals of Neurology 2016

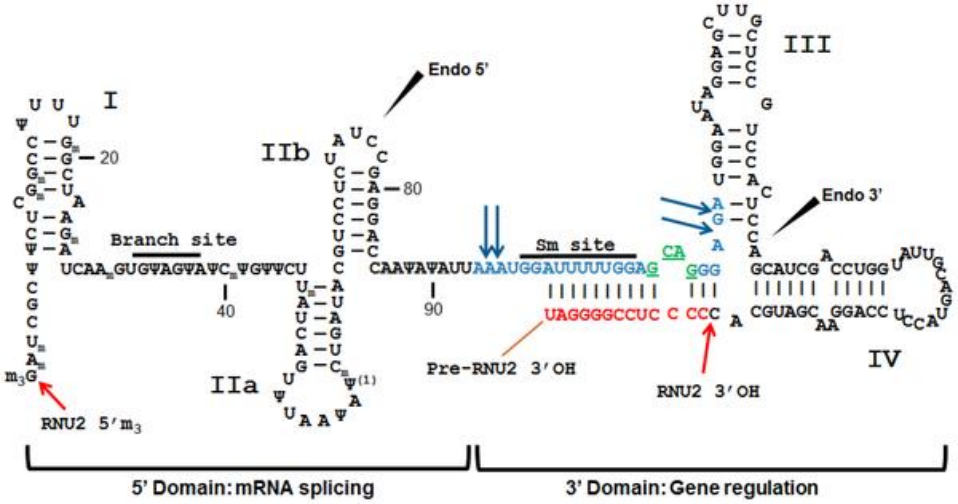
How can two phenotypes be causes by biallelic variants in the same gene?

RNU12: an obligate 3’ extension variant in CDAGS



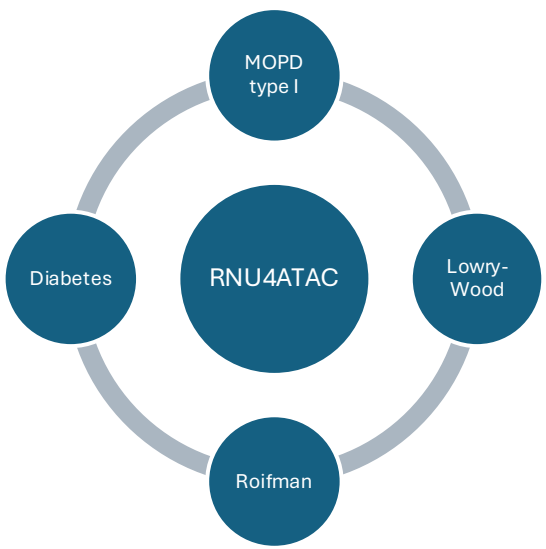
Xing et al. Human Mutation 2021

U2 – the major spliceosome equivalent of U12

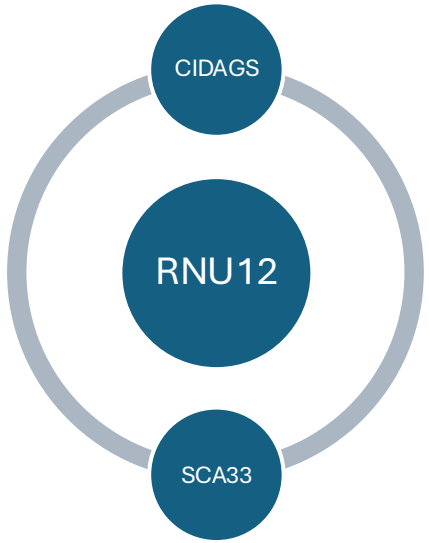


Mazieres et al. PLoS One. 2013

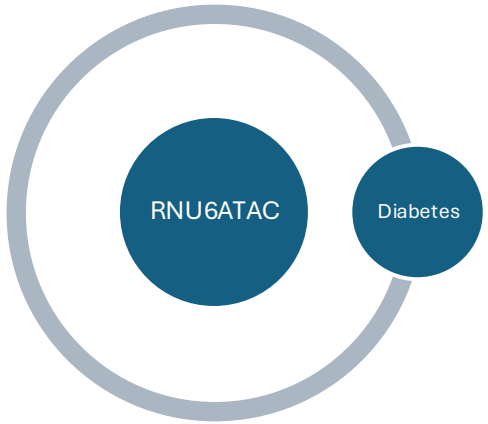
Summary of minor RNUopathies



RNU4ATAC-opathy spectrum



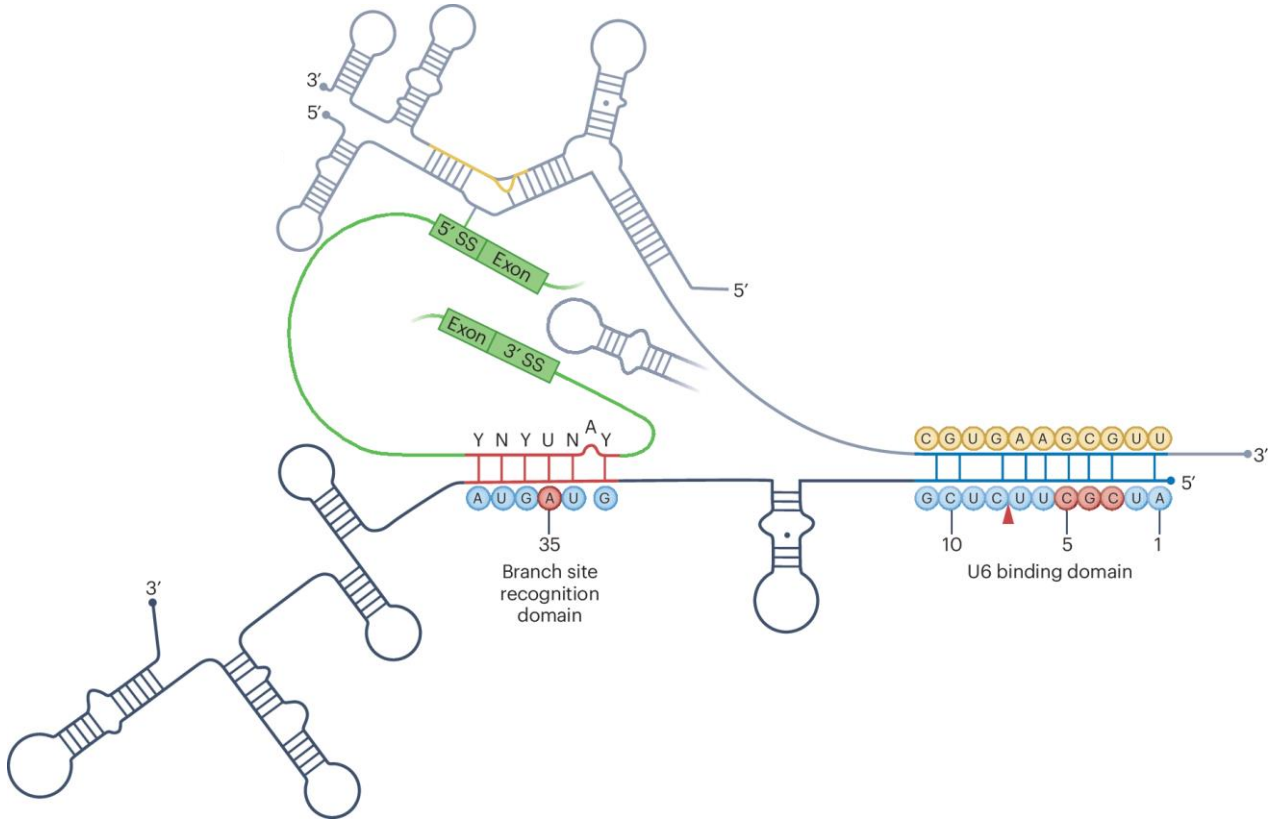
Likely distinct disease mechanisms



Awaiting further phenotypic characterisation

What about the major spliceosome?

snRNAs of major spliceosome and dominant NDD



Antonarakis. Nat Genet. 2026

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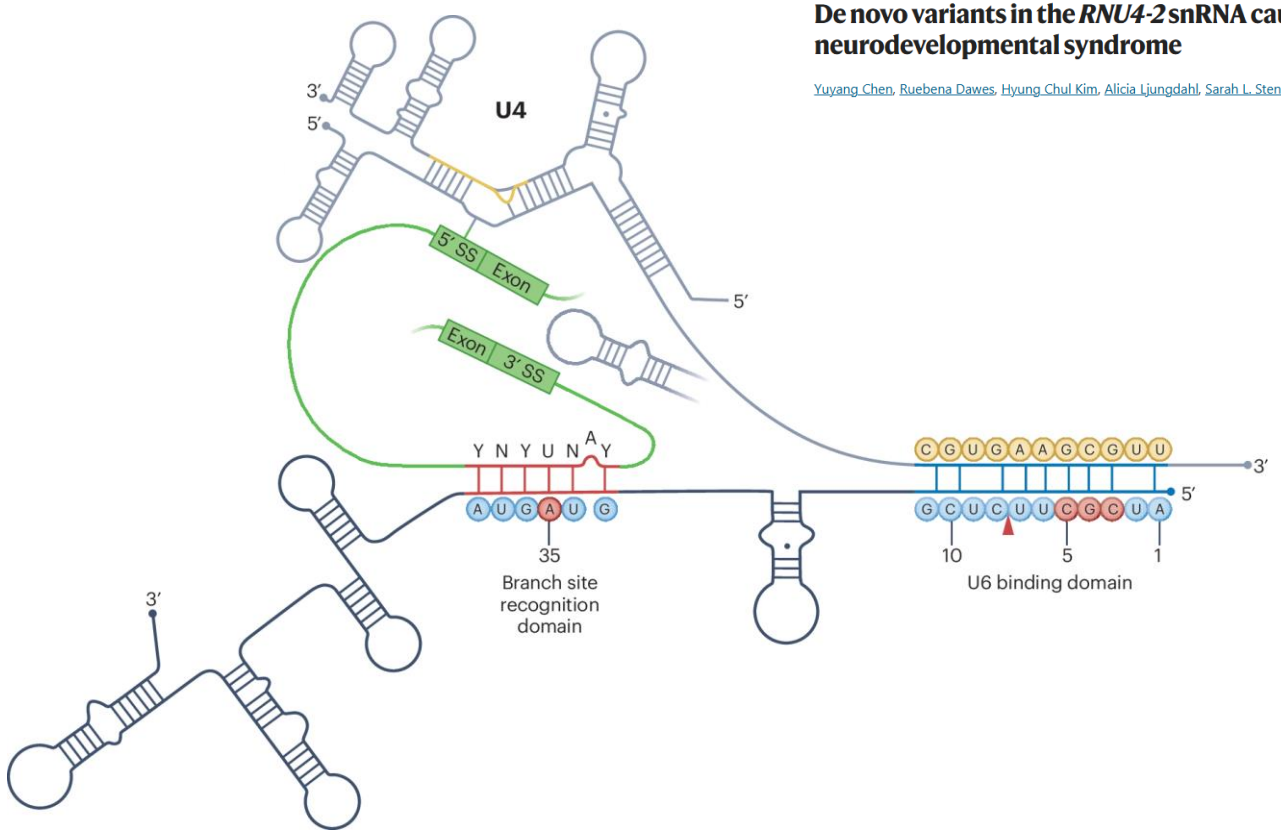

Article | Open access | Published: 11 July 2024

De novo variants in the *RNU4-2* snRNA cause a frequent neurodevelopmental syndrome

Yuyang Chen, Ruebena Dawes, Hyung Chul Kim, Alicia Ljungdahl, Sarah L. Stenton, Susan Walker, Jenny

Brief Communication | Open access | Published: 31 May 2024

Mutations in the U4 snRNA gene *RNU4-2* cause one of the most prevalent monogenic neurodevelopmental disorders

Daniel Greene, Chantal Thys, Ian R. Berry, Joanna Jarvis, Els Ortibus, Andrew D. Mumford, Kathleen Freson

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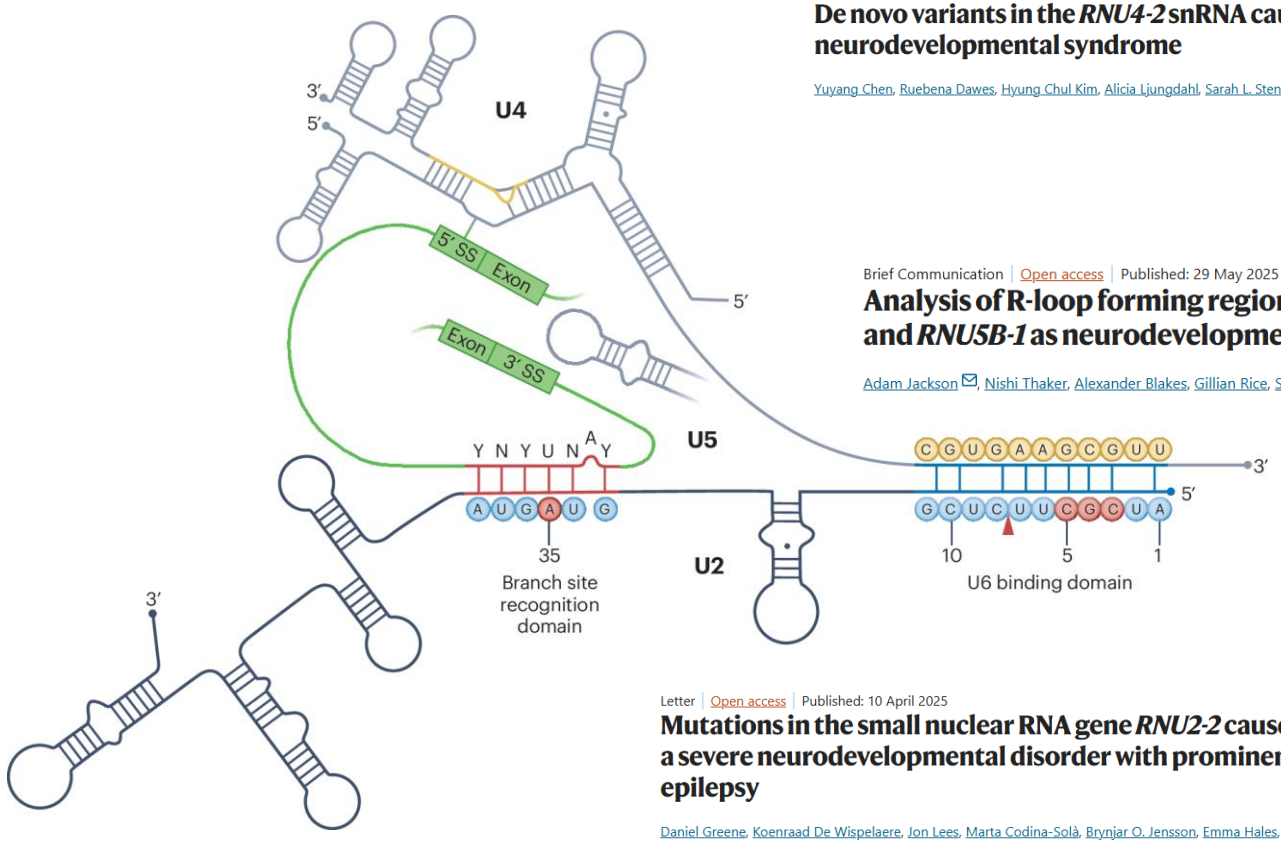

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Brief Communication | Open access | Published: 29 May 2025

Analysis of R-loop forming regions identifies *RNU2-2* and *RNU5B-1* as neurodevelopmental disorder genes

Adam Jackson, Nishi Thaker, Alexander Blakes, Gillian Rice, Sam Griffiths-Jones, Meena

Article | Open access | Published: 16 May 2025

Dominant variants in major spliceosome U4 and U5 small nuclear RNA genes cause neurodevelopmental disorders through splicing disruption

Caroline Nava, Benjamin Cogne, Amandine Santini, Elsa Leitão, François Lecoquierre, Yuyang Chen,

Letter | Open access | Published: 10 April 2025

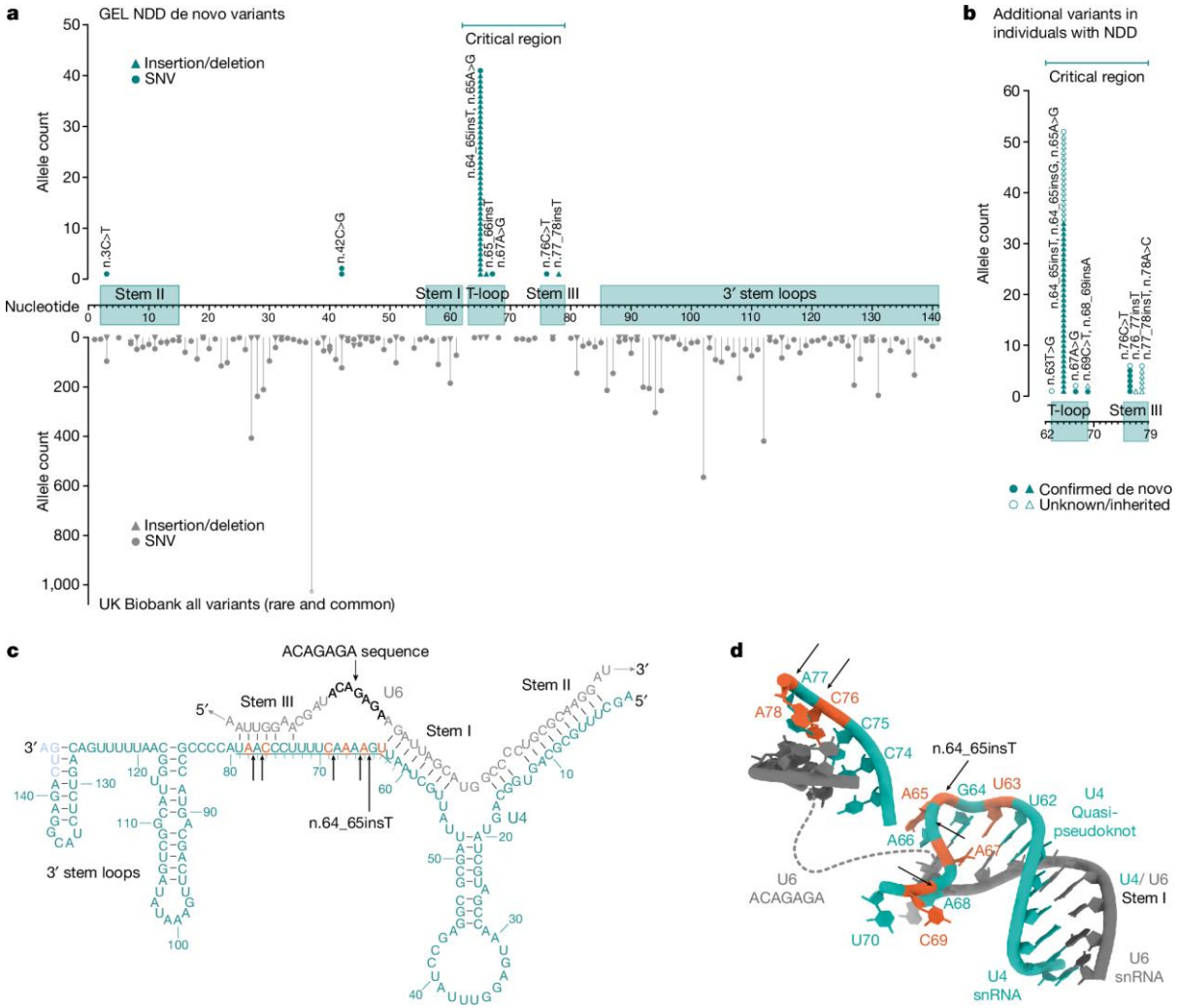
Mutations in the small nuclear RNA gene *RNU2-2* cause a severe neurodevelopmental disorder with prominent epilepsy

Daniel Greene, Koenraad De Wispelaere, Jon Lees, Marta Codina-Solà, Brynjar O. Jensson, Emma Hales,

Antonarakis. Nat Genet. 2026

Dominant RNU4-2 neurodevelopmental disorder (141bp)

ReNU syndrome





Chen et al. Nature. 2024

Dominant RNU4-2 neurodevelopmental disorder (141bp)

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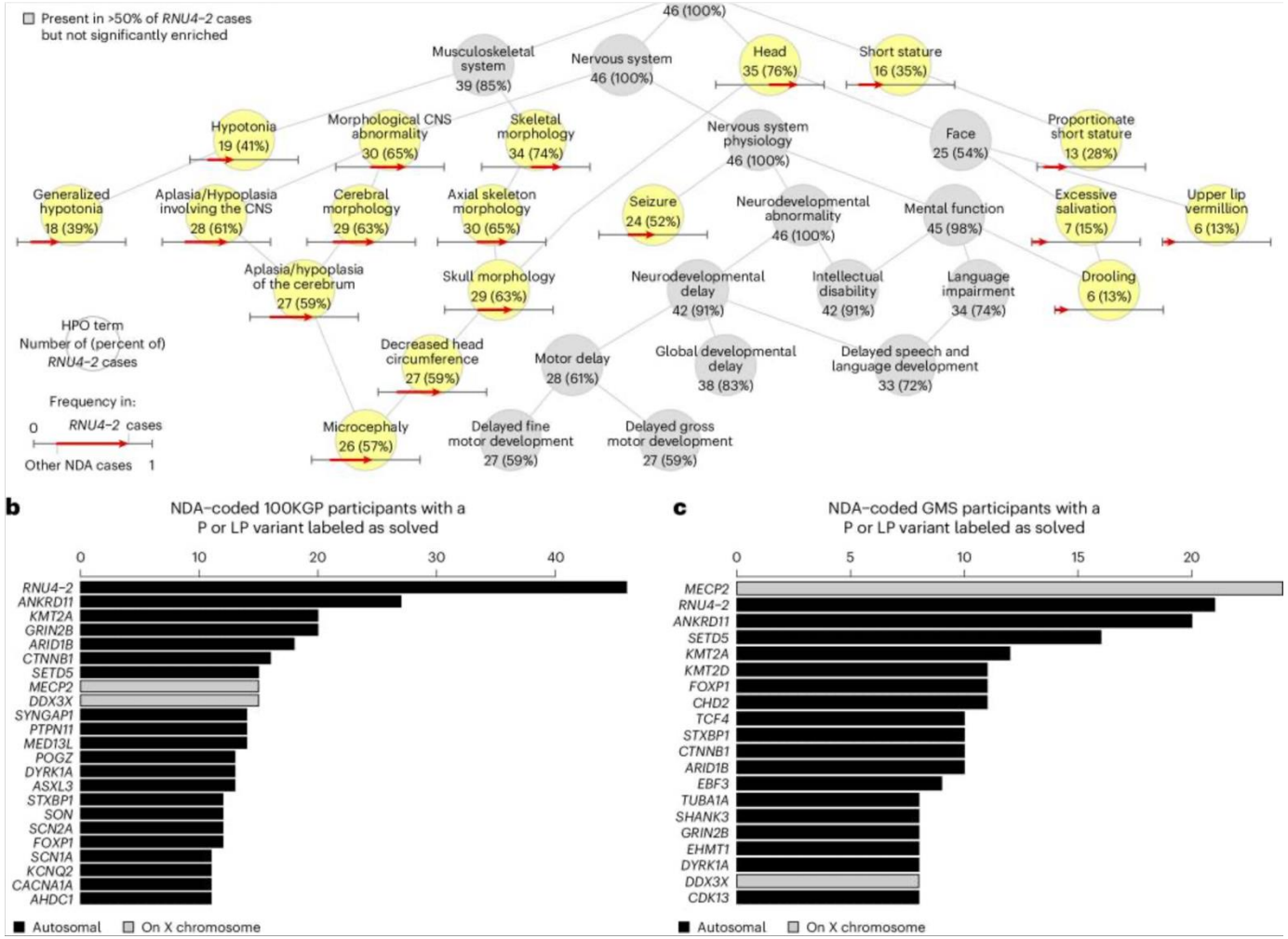
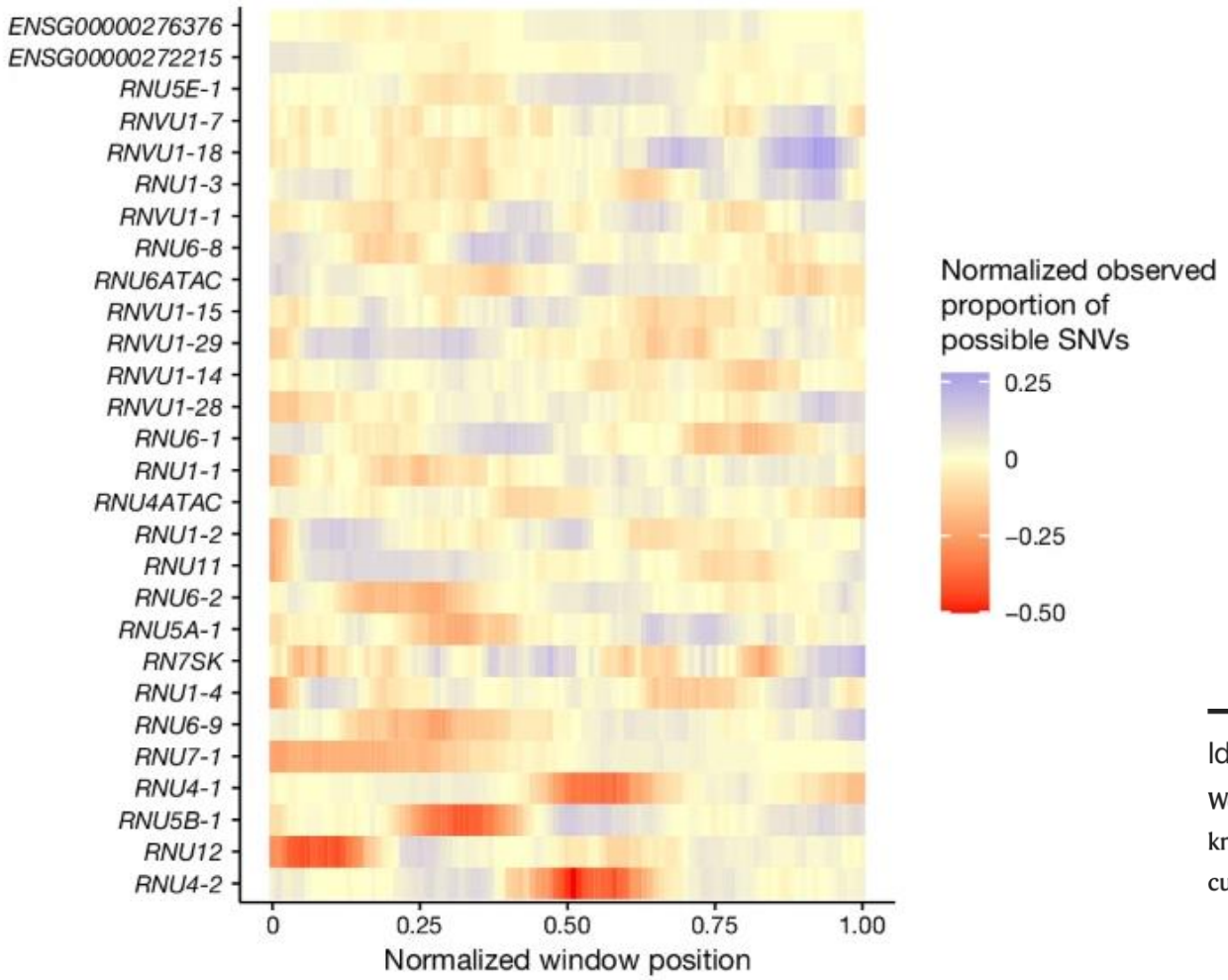
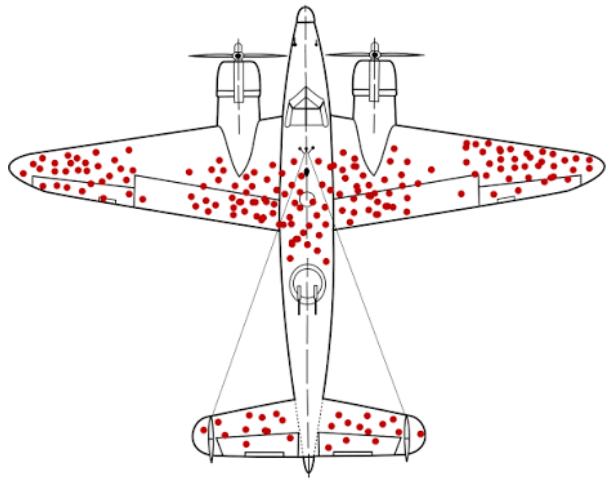


Could there be other dominant RNUopathies?

Greene et al. Nat Genet. 2024

Dominant RNU4-2 neurodevelopmental disorder (141bp)





Identifying human snRNA genes

We extracted genes with snRNA biotypes from Ensembl genome annotation v.111. We filtered out known pseudogenes (that is, with gene names marked with 'P' or identified through manual curation). For each remaining gene, we used BrainVar[23] RNA-seq expression data to calculate the

What is a pseudogene?

Chen et al. Nature. 2024

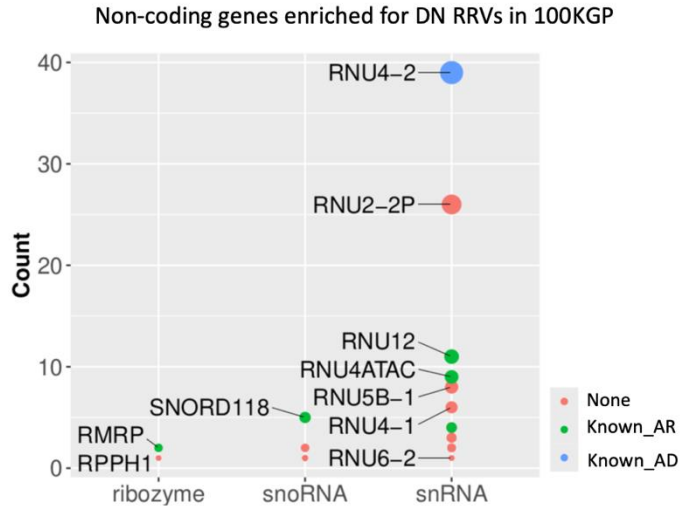
Dominant RNU4-2 neurodevelopmental disorder (141bp)

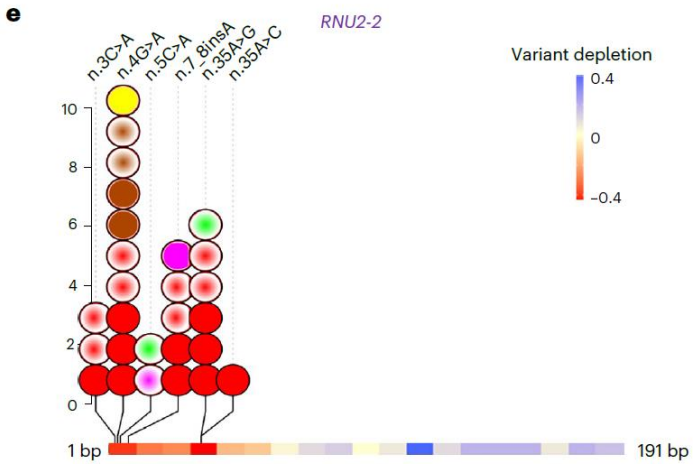
pseudogene	Have homology to proteins but generally suffer from a disrupted coding sequence and an active homologous gene can be found at another locus. Sometimes these entries have an intact coding sequence or an open but truncated ORF, in which case there is other evidence used (for example genomic polyA stretches at the 3' end) to classify them as a pseudogene. Can be further classified as one of the following.

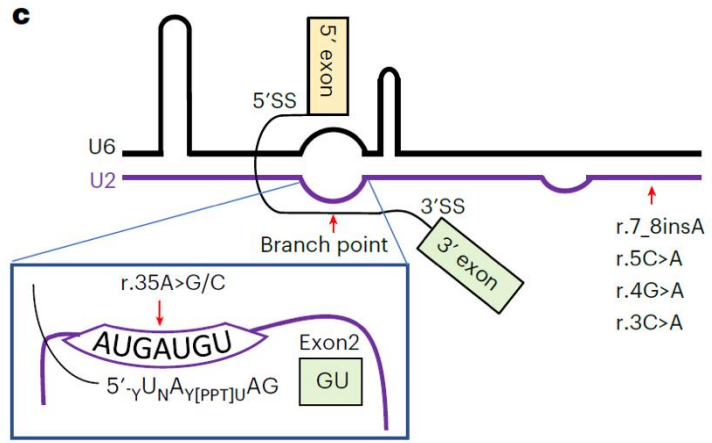
Can this be used w.r.t a non-coding gene?

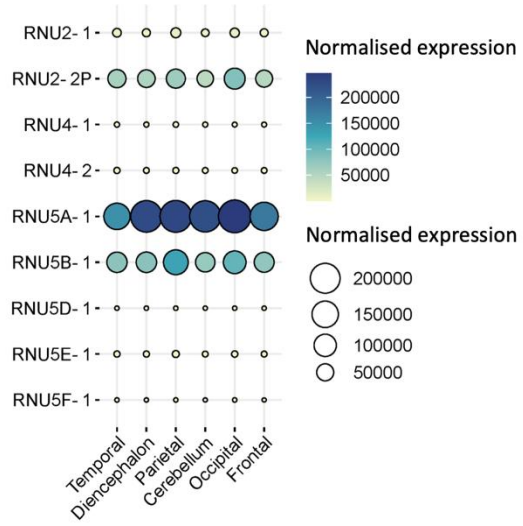
Chen et al. Nature. 2024

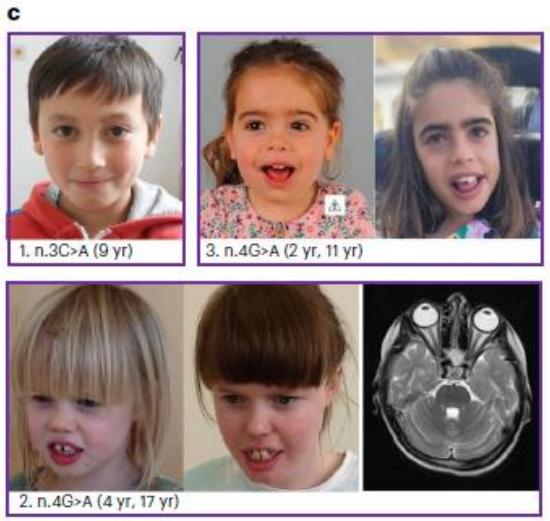
Dominant RNU2-2 (P) neurodevelopmental disorder (191bp)

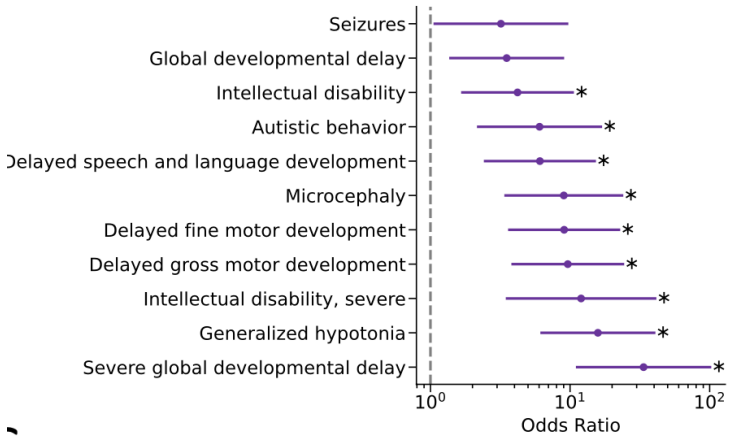










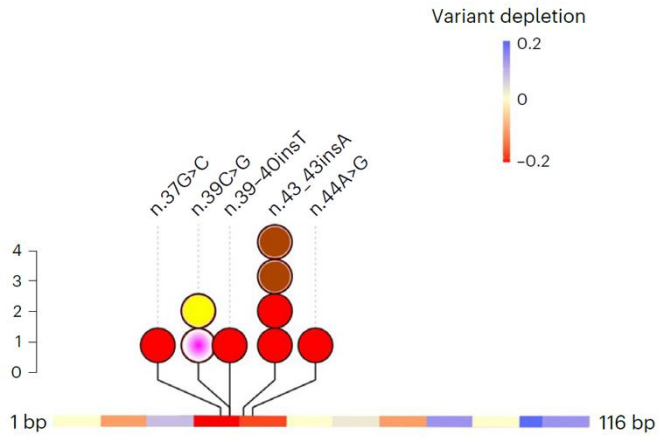


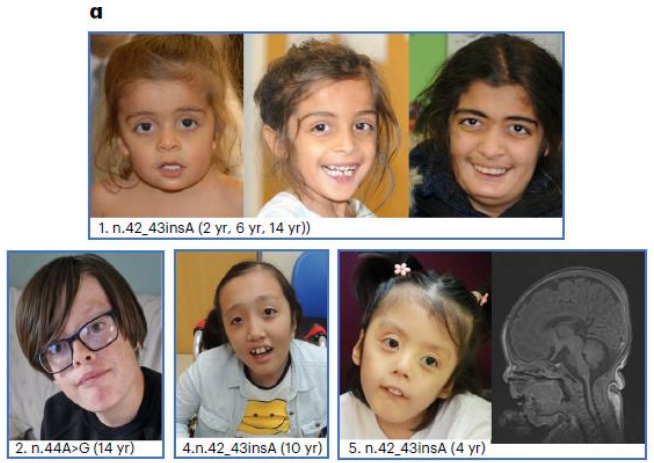
What if the stringency for de novo filtering is relaxed?

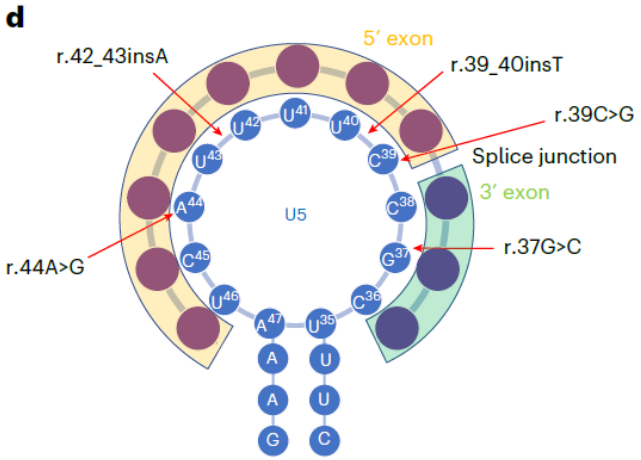
Jackson et al. Nat Genet. 2025

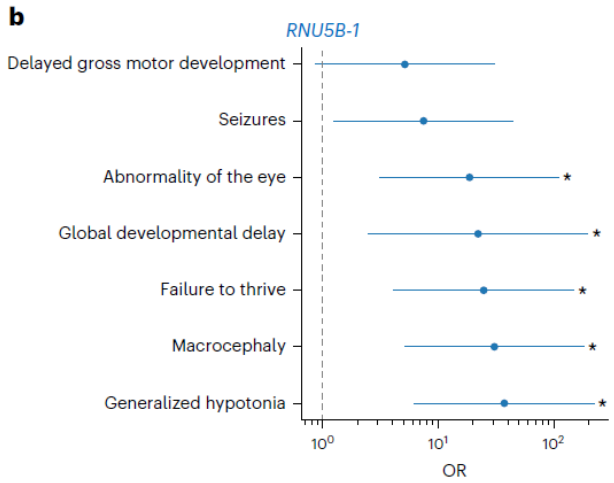
RNU5B-1 neurodevelopmental disorder (116bp)

The only shared component of the major and minor spliceosome





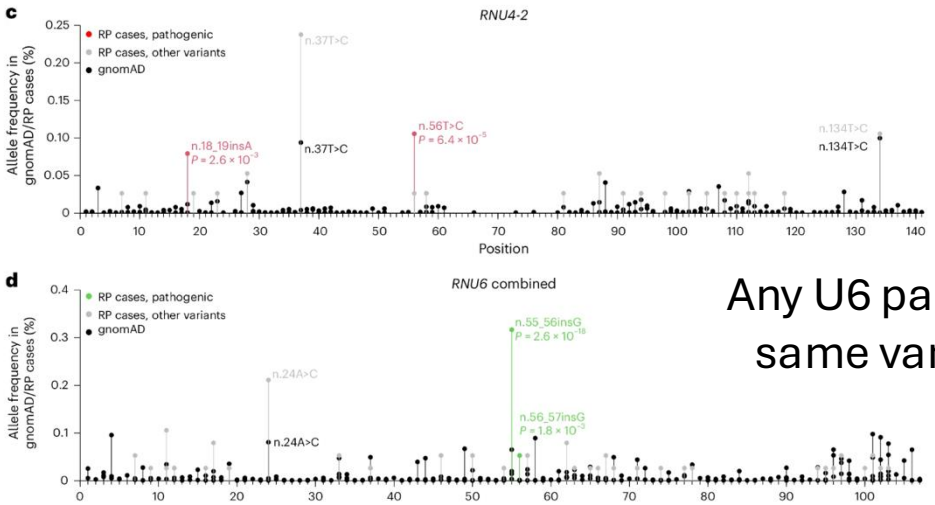




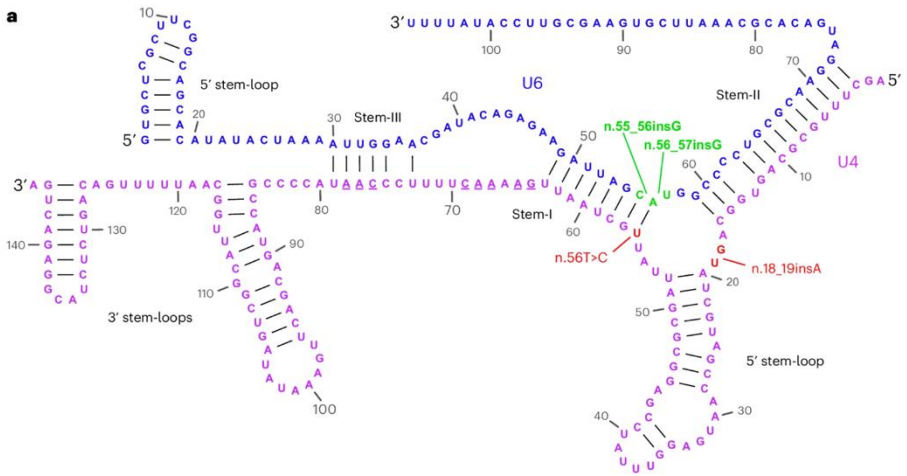
What about other phenotypes?

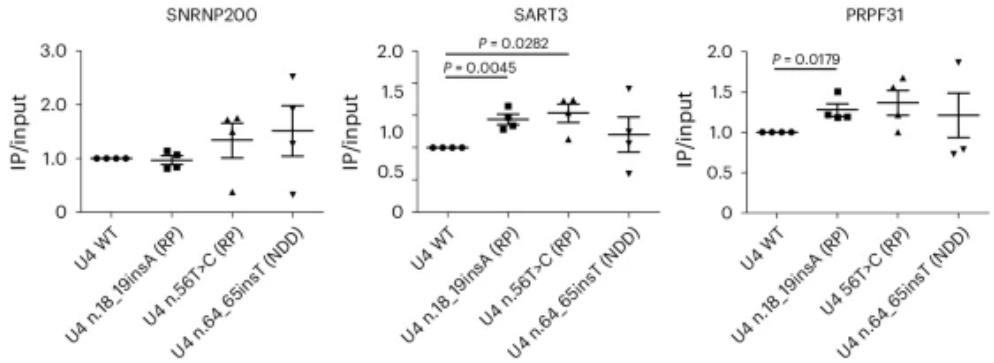
Jackson et al. Nat Genet. 2025

snRNAs of major spliceosome emerge as prominent causes of dominant RP



Any U6 paralog, same variant



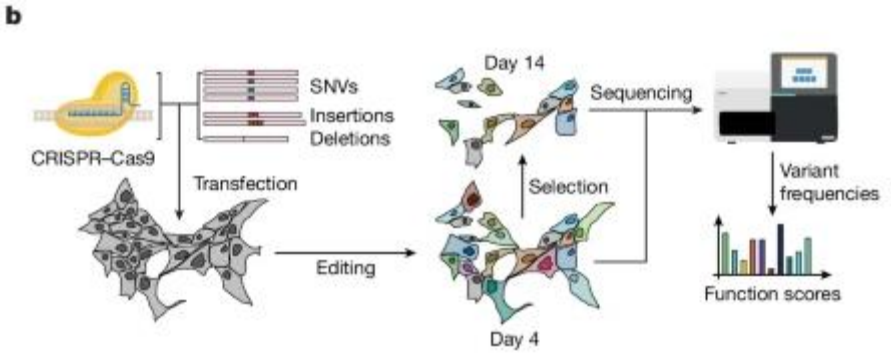


*RP variants affect snRNP assembly, whilst NDD variants do not

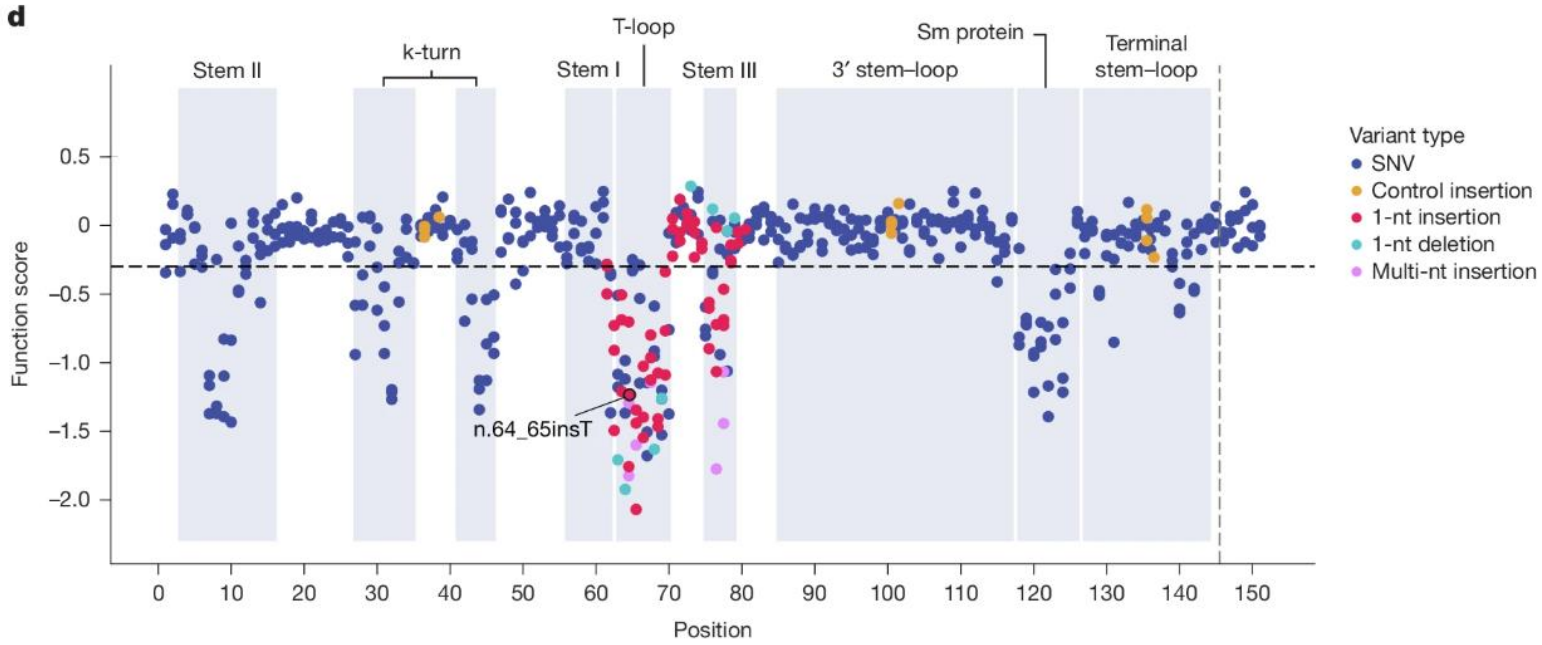
How can pathogenic variants in non-coding RNAs be identified?

Quinodoz et al. Nat Genet. 2026

Saturation genome editing suggests complexity in RNU4-2



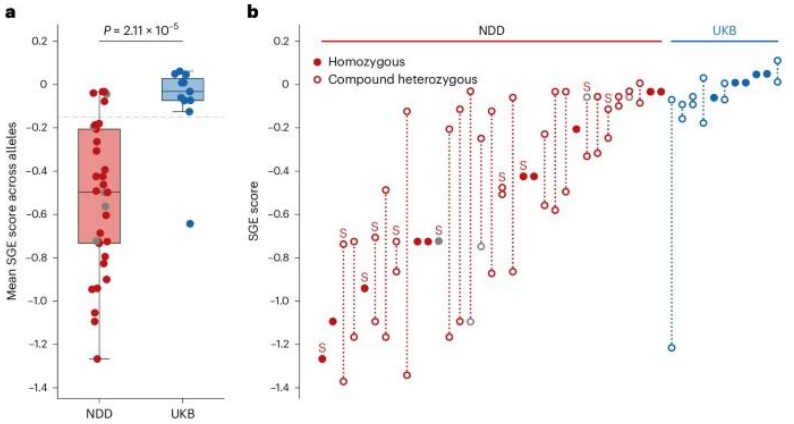


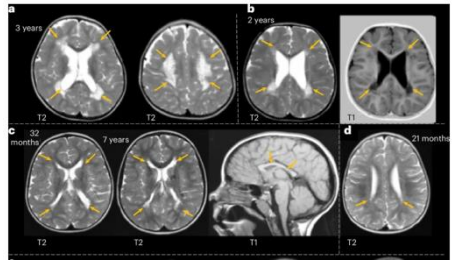


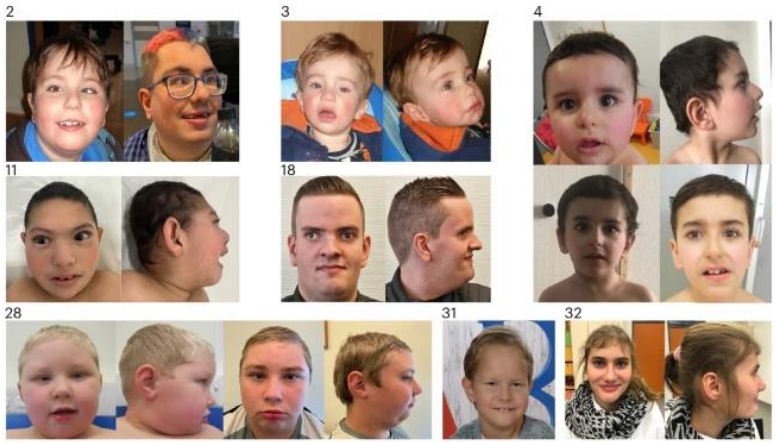
What about these depleted non-T-loop variants?

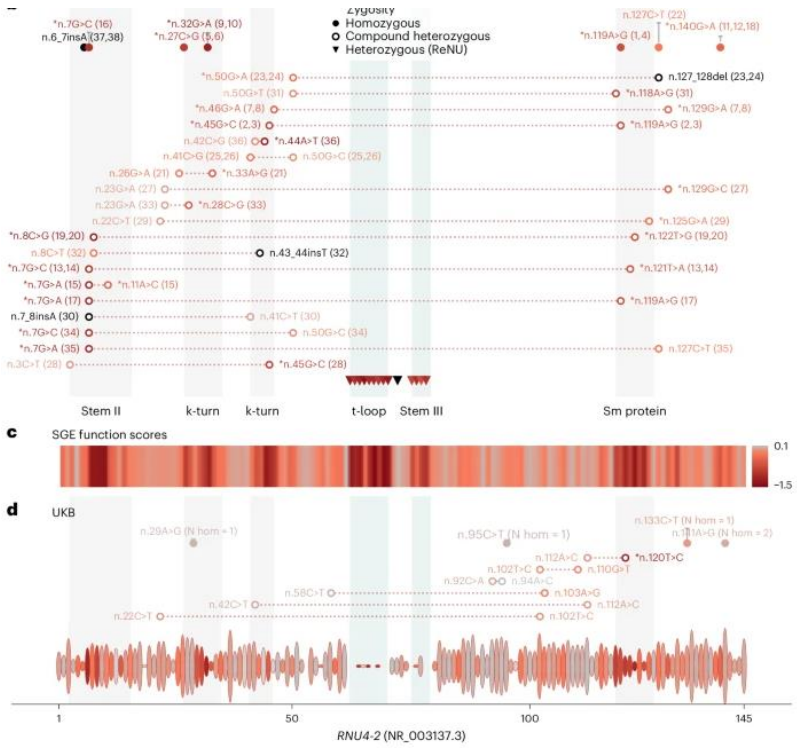
De Jonghe et al. Nature. 2026.

Recessive RNU4-2 neurodevelopmental disorder









Are there other recessive major RNUopathies?

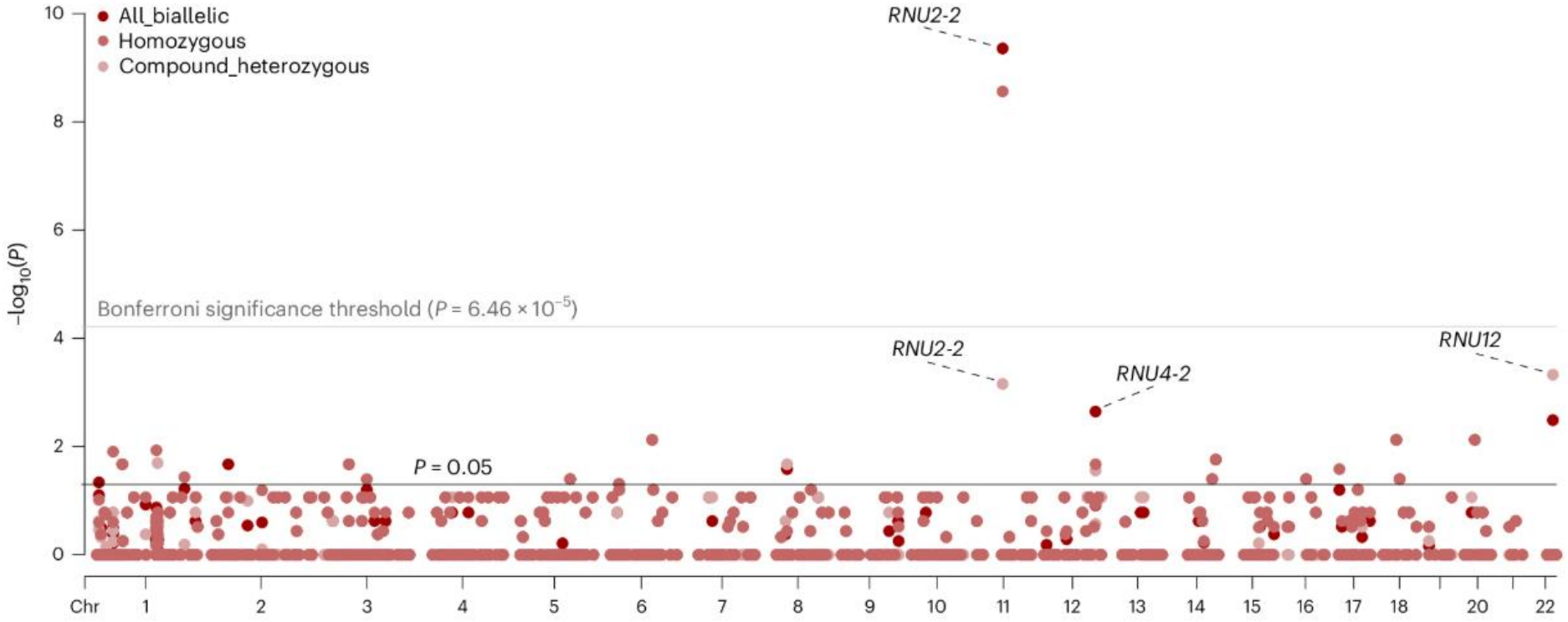
Rius et al. Nat Genet. 2026.

Recessive RNU2-2 neurodevelopmental disorder



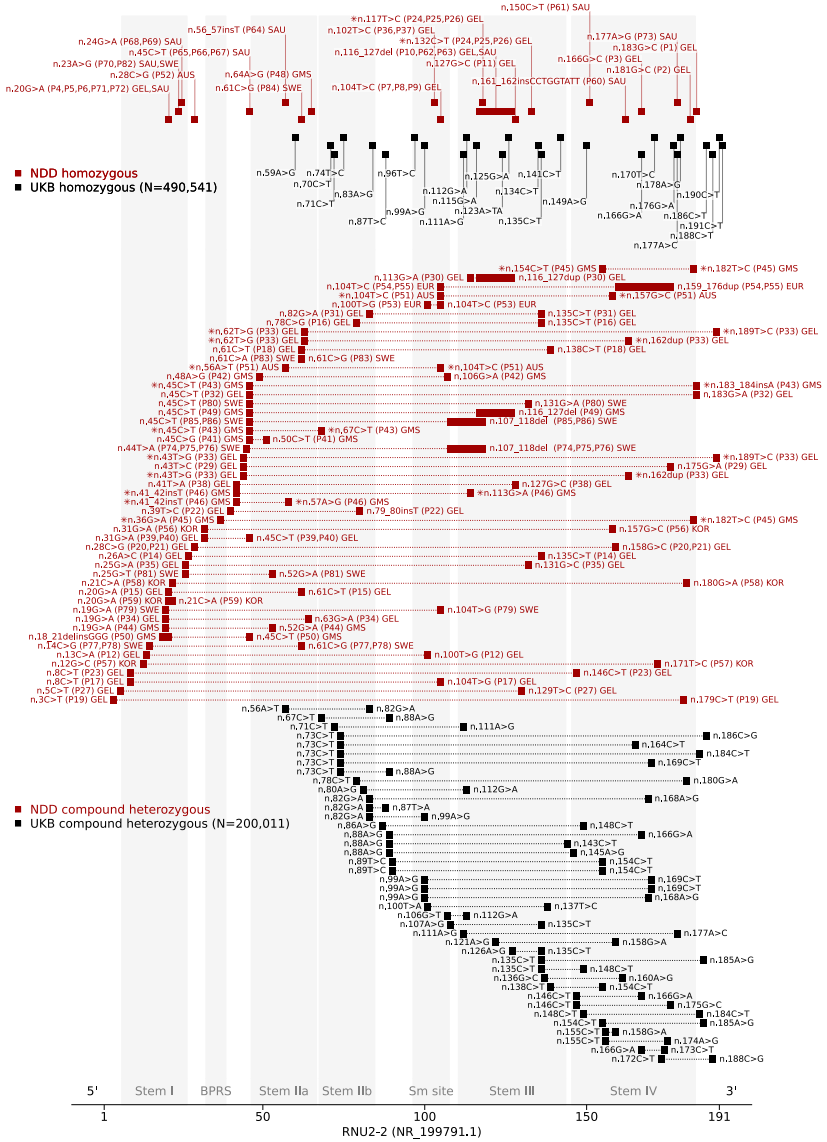
Unsolved NDD
(n=6762)

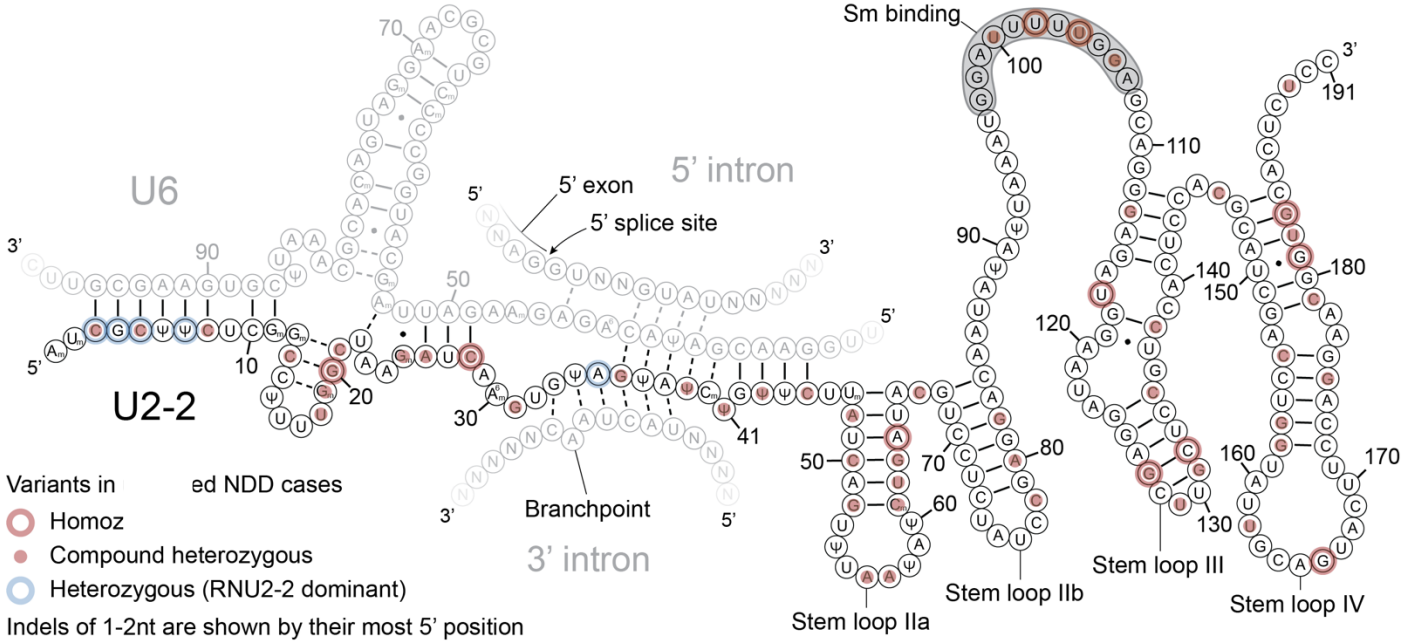
Controls
(n=71289)



Jackson and Blakes et al. Nat Genet. 2026

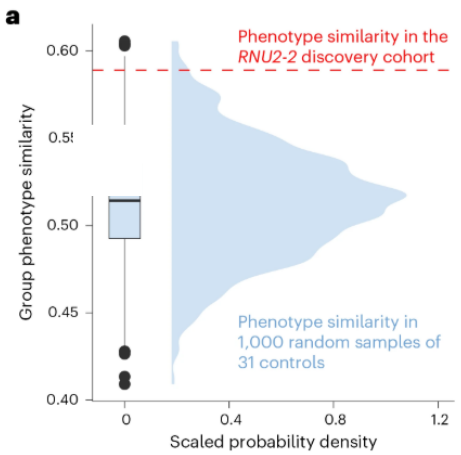
Recessive RNU2-2 neurodevelopmental disorder

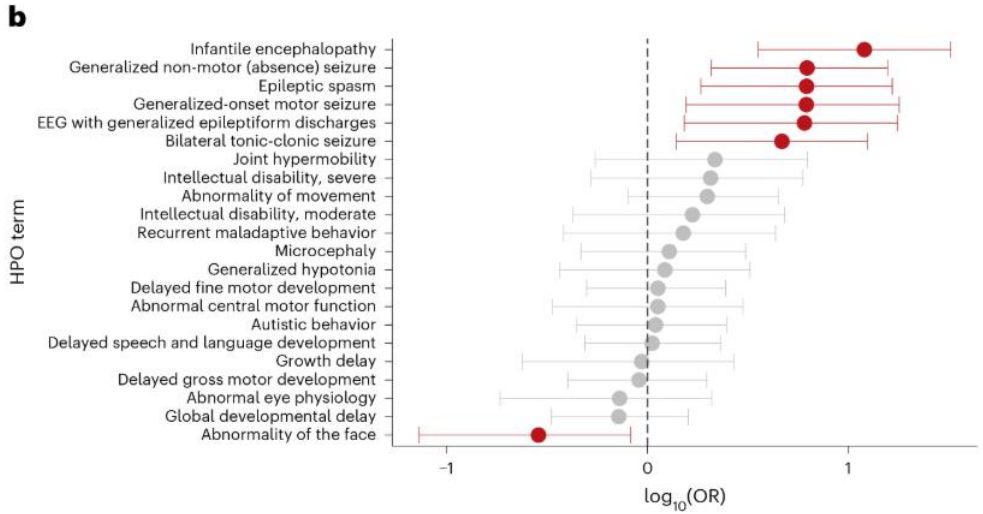




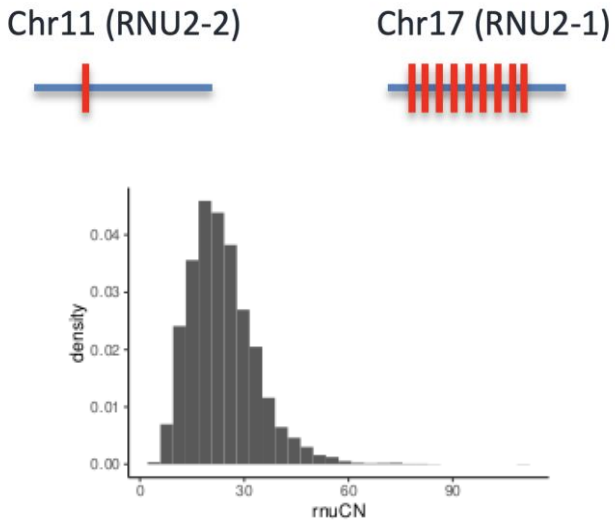
Jackson and Blakes et al. Nat Genet. 2026

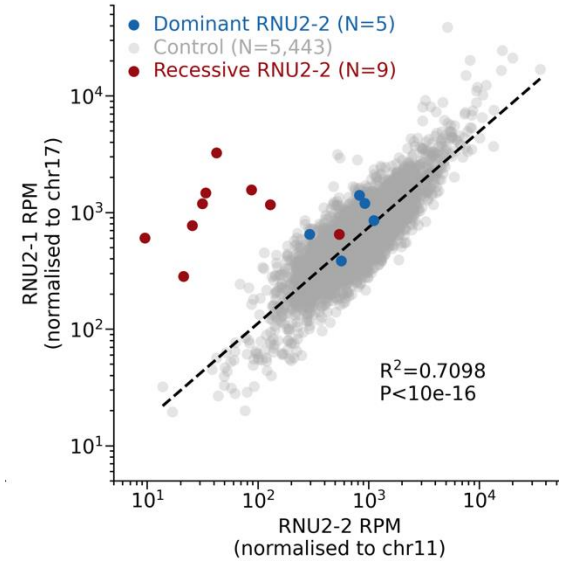
Recessive RNU2-2 neurodevelopmental disorder

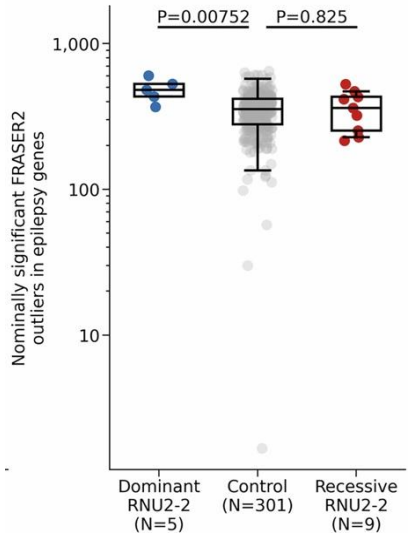








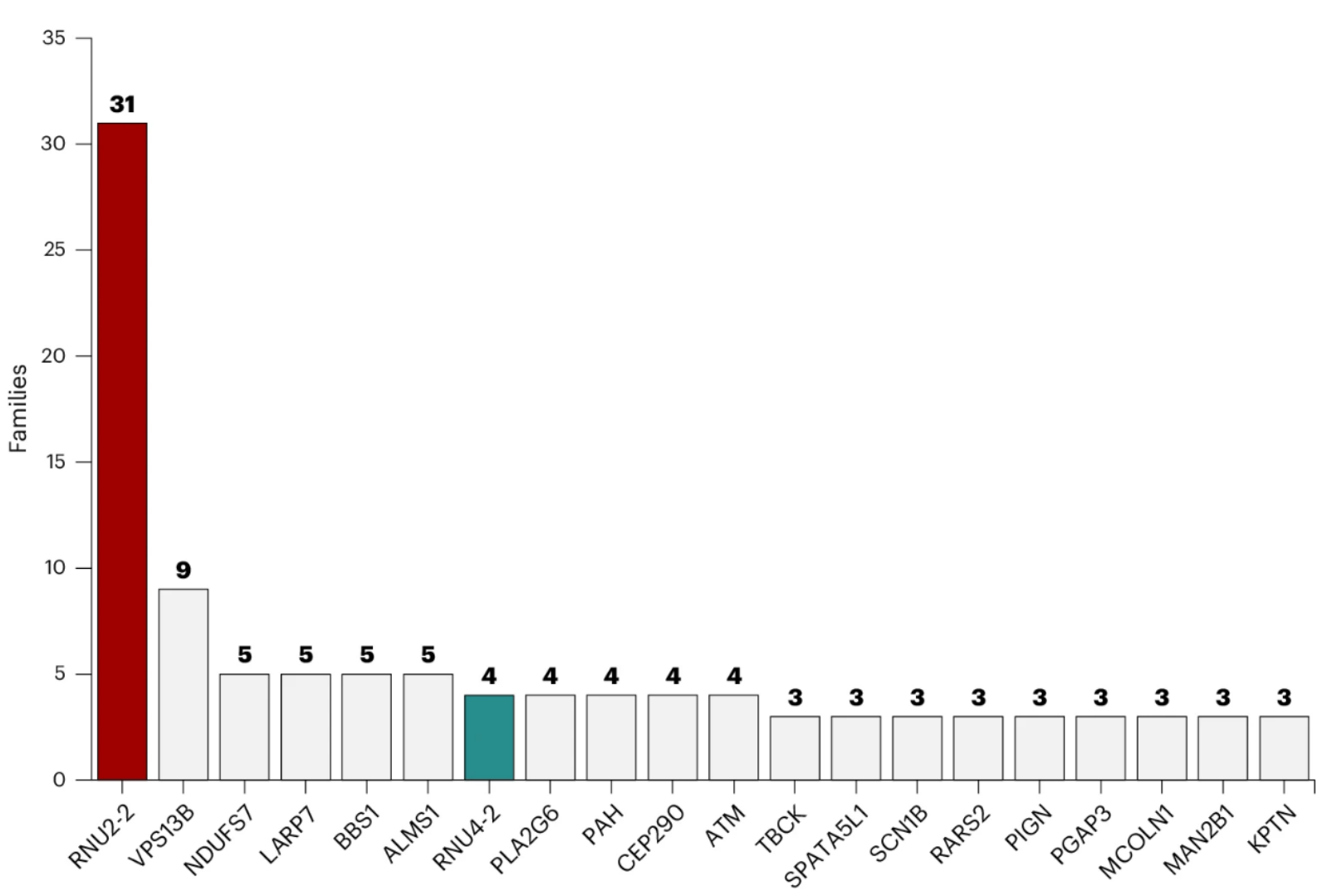




How common are major RNUopathies?

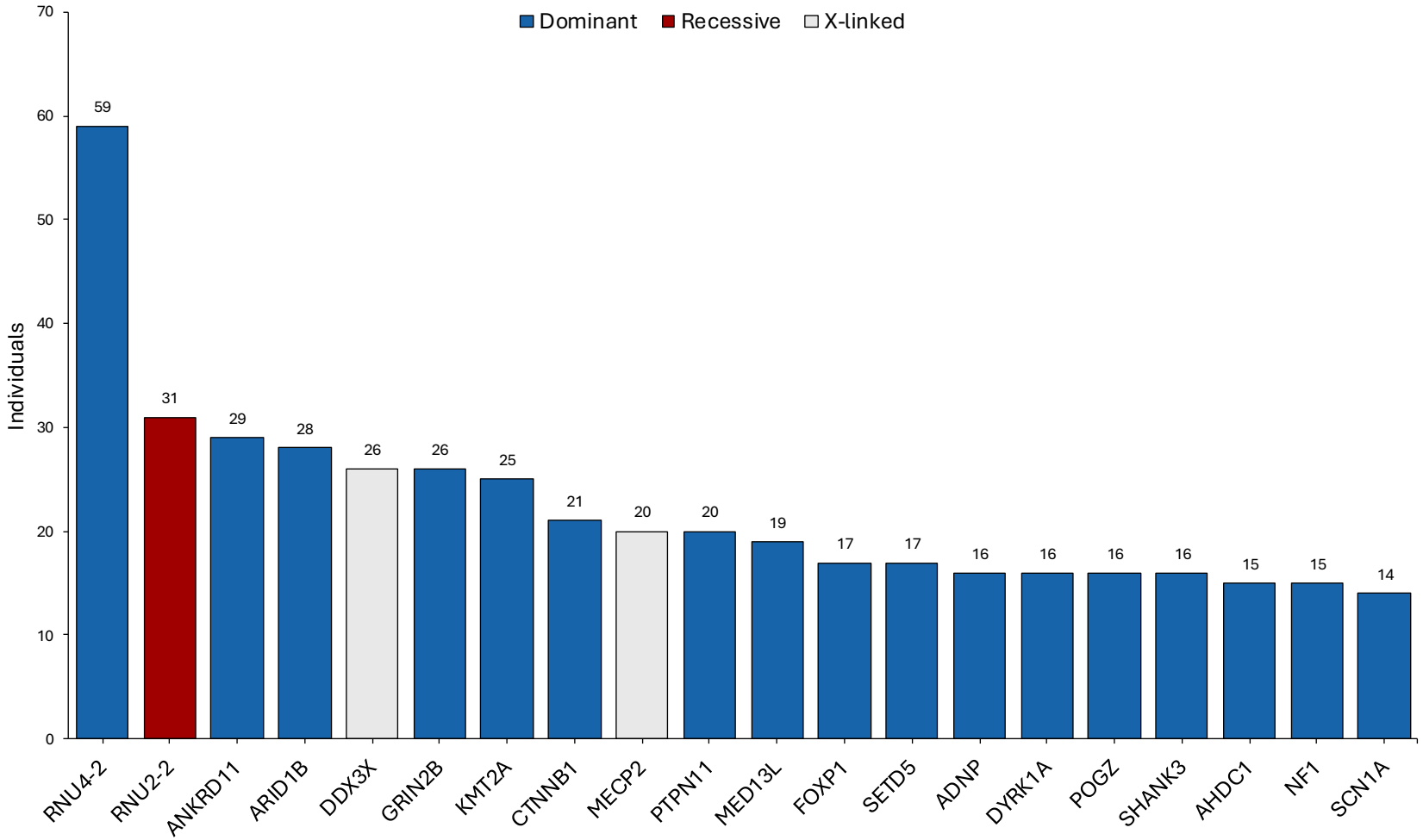
Jackson and Blakes et al. Nat Genet. 2026

Recessive *RNU2-2* is the commonest recessive NDD in 100KGP



Jackson and Blakes et al. Nat Genet. 2026

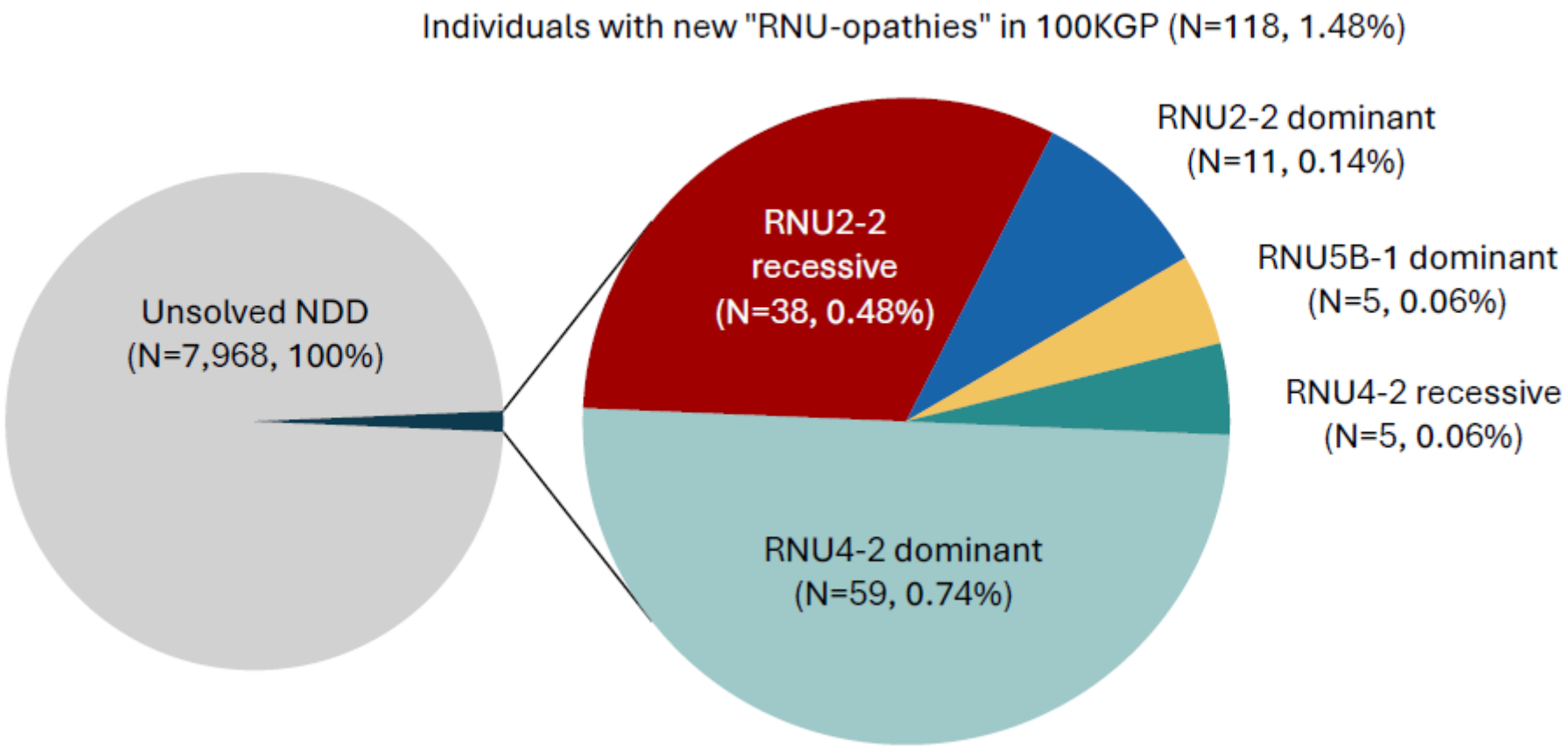
The burden of RNUopathies in neurodevelopmental disorders



What is the contribution of all novel RNUopathies to unsolved NDD?

Jackson and Blakes et al. Nat Genet. 2026

The burden of RNUopathies in neurodevelopmental disorders



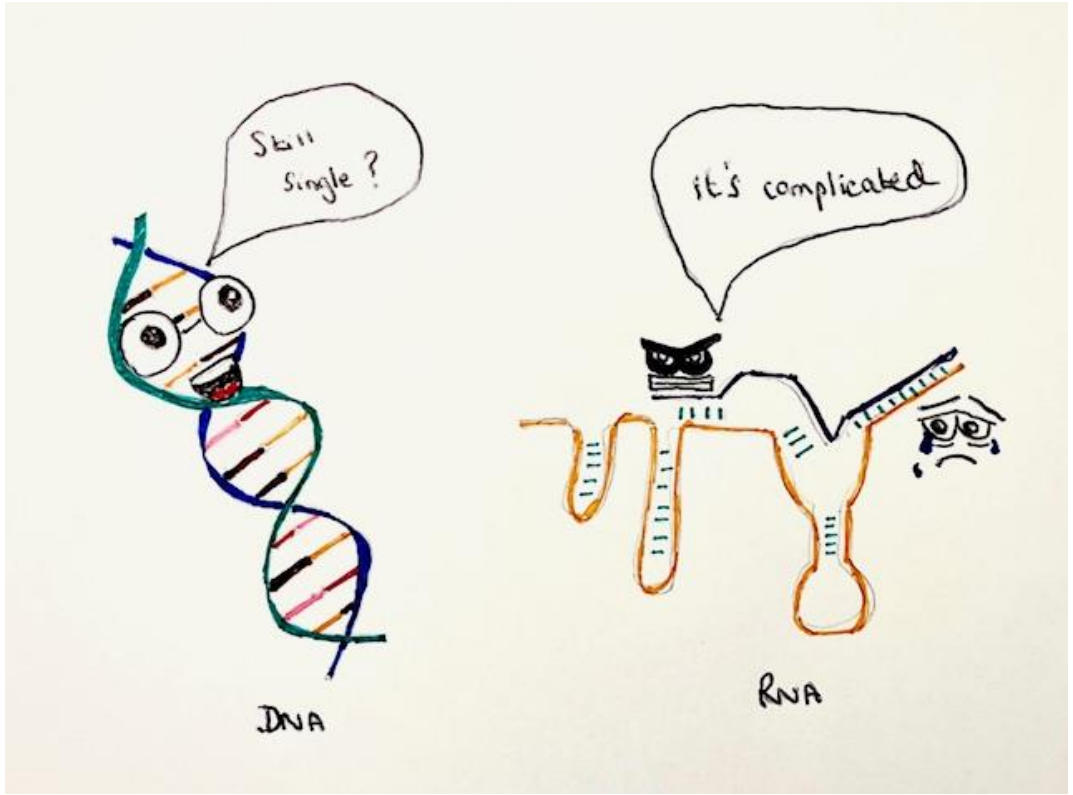
The 100,000 Genomes Project

Jackson and Blakes et al. Nat Genet. 2026

Summary

- snRNAs are non-coding components of the spliceosome
- There are likely ~200 snRNAs in the human genome which are active
- **Dominant** disorders are caused frequently by de novo variants in **constrained** regions of these genes
  - Haploinsufficiency is unlikely a disease mechanism for these genes
- **Recessive** disorders are associated with biallelic variants which often reduce **transcript abundance**
- Variant interpretation is made challenging by:
  - Wide phenotypic spectrum in recessive disorders (?distinct disorders with distinct mechanisms)
  - Lack of *in silico* predictors and biomarkers
  - High mutability of these genes – highly likely to harbor de novo variants

Manchester RNU clinic – please refer



Thank you for listening. Any questions?

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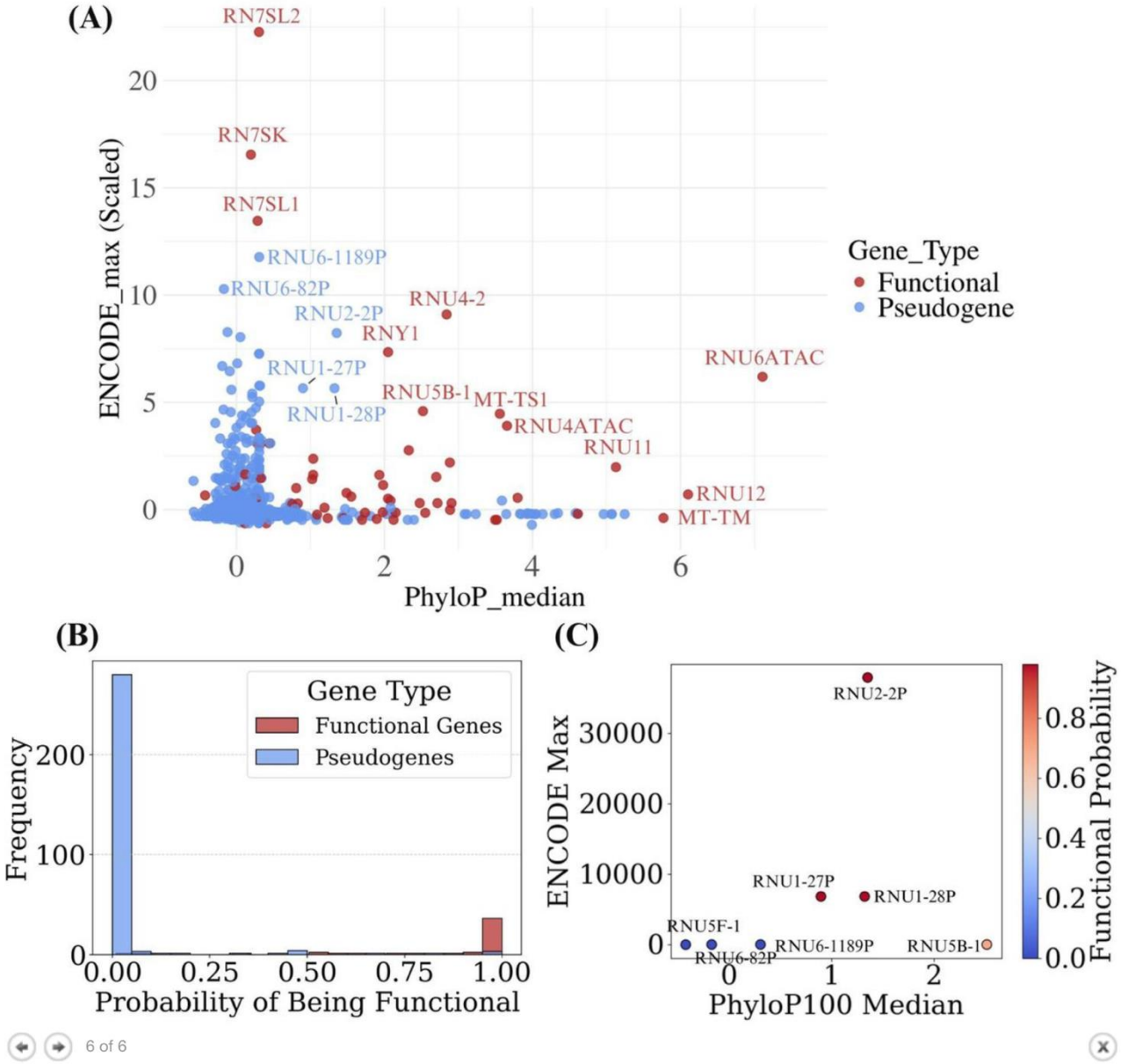
Other bogus ’P’ annotations



Prasetyo et al. bioRxiv. 2024

The snRNAs of the major and minor spliceosomes

Spliceosome	snRNA (size)	Genes (location)	Diseases	Inheritance
Major	U1 (163 bp)	*RNU1* (Chr 1, 30 copies)	None	NA
	U2 (191 bp)	*RNU2-1* (Chr 17, 5 – 82 copies)	None	NA
		RNU2-2 (Chr 11)	***RNU2-2*-related DEE**	**AD**
			***RNU2-2*-related DEE**	**AR**
	U4 (141 bp)	*RNU4-1* (Chr 12)	None	NA
		RNU4-2 (Chr 12)	***RNU4-2*-related ReNU syndrome**	**AD**
			***RNU4-2*-related NDD**	**AR**
			***RNU4-2*-related retinal dystrophy**	**AD**
	U6 (107 bp)	*RNU6-1* (Chr 15)	***RNU6-1*-related retinal dystrophy**	**AD**
		RNU6-2 (Chr 19)	***RNU6-2*-related retinal dystrophy**	**AD**
		RNU6-7 (Chr 14)	None	NA
		RNU6-8 (Chr 14)	***RNU6-8*-related retinal dystrophy**	**AD**
		RNU6-9 (Chr 19)	***RNU6-9*-related retinal dystrophy**	**AD**
Both	U5 (116 bp)	*RNU5A-1* (Chr 15)	None	NA
		RNU5B-1 (Chr 3)	***RNU5B-1*-related NDD syndrome**	**AD**
		RNU5D-1 (Chr 1)	None	NA
		RNU5E-1 (Chr 1)	None	NA
		RNU5F-1 (Chr 1)	None	NA
Minor	U11 (134 bp)	*RNU11* (Chr 1)	None	NA
	U12 (150 bp)	*RNU12* (Chr 22)	***RNU12*-related CDAGS syndrome**	**AR**
			***RNU12*-related SCA33?**	**AR**
	U4atac (127 bp)	*RNU4ATAC* (Chr 2)	***RNU4ATAC*-related Lowry-Wood syndrome**	**AR**
			***RNU4ATAC*-related Type 1 MOPD**	**AR**
			***RNU4ATAC*-related Roifman syndrome**	**AR**
	U6atac (126 bp)	*RNU6ATAC* (Chr 9)	None	NA

* **Bold** = disease associated genes; **Red** = novel RNUopathy; **Grey** = RP phenotype