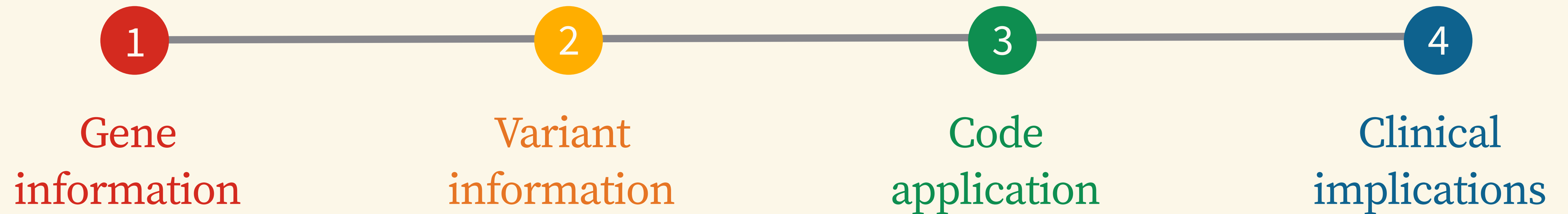


29 MAY 2026

SF3B1:c.2098A>G p.(Lys700Glu)

Tumour board presentation

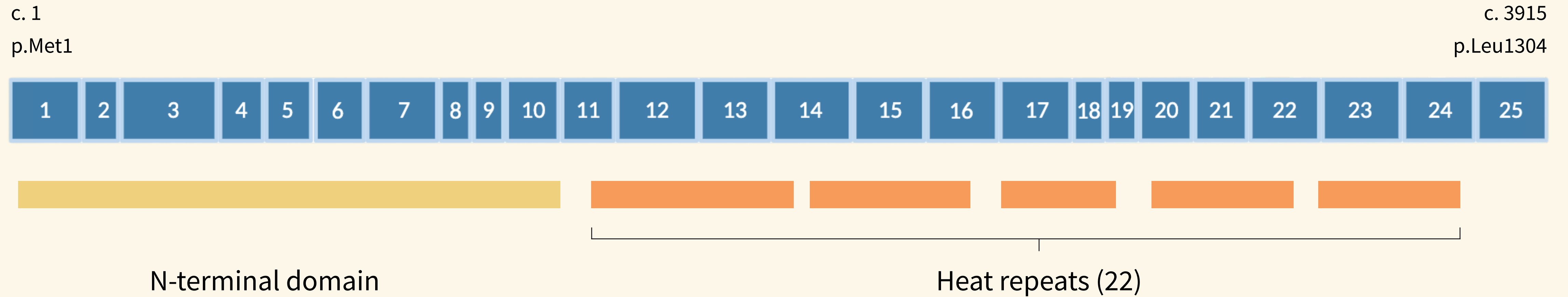
content



Gene information

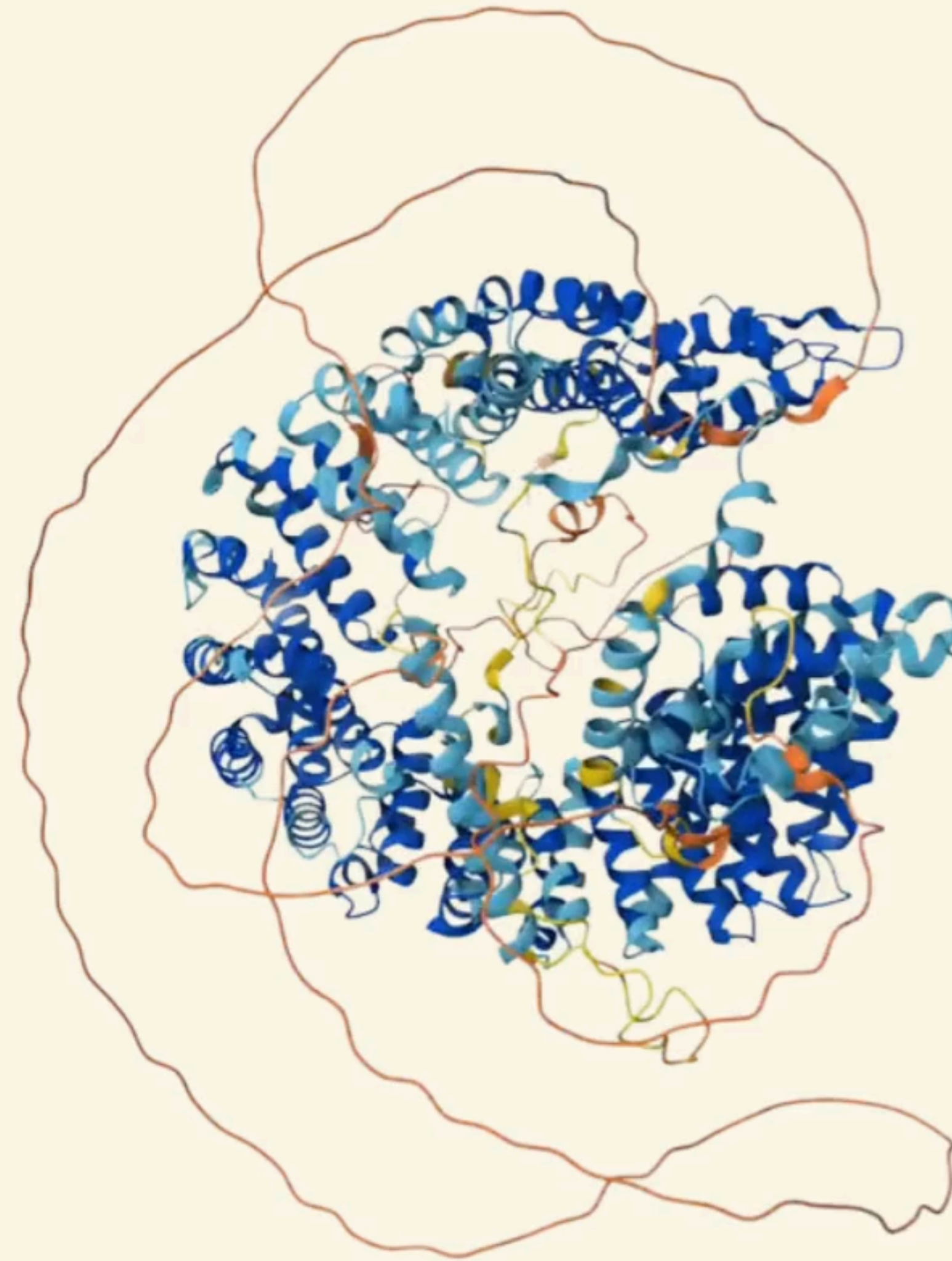
SF3B1

Splicing Factor 3b Subunit 1

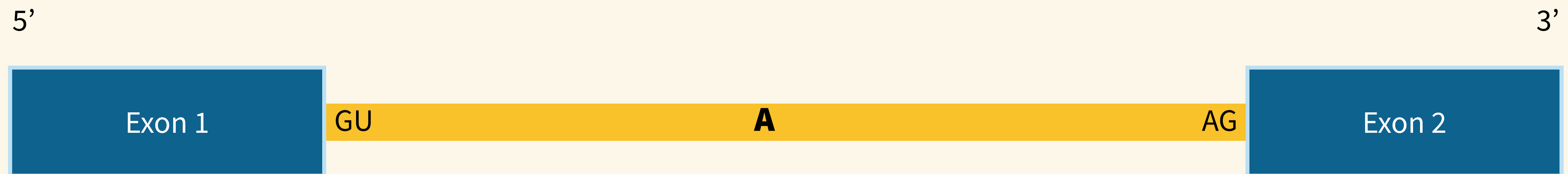


SF3B1

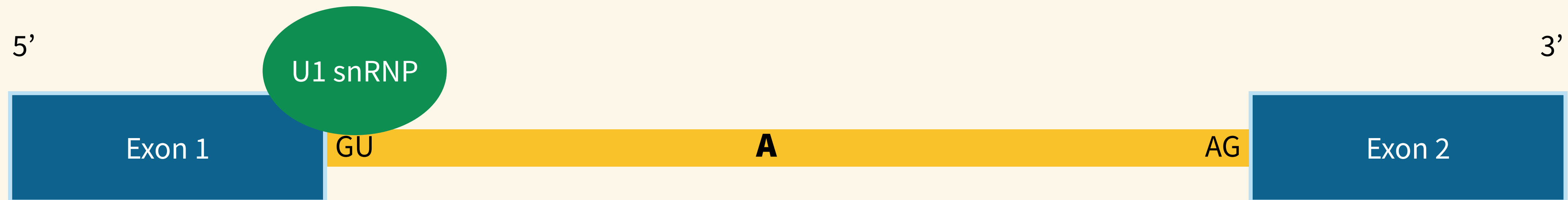
Splicing Factor 3b Subunit 1



Spliceosome complex

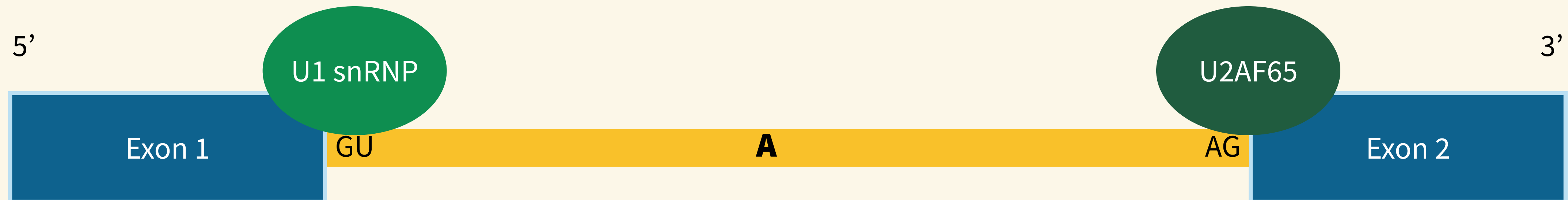


Spliceosome complex



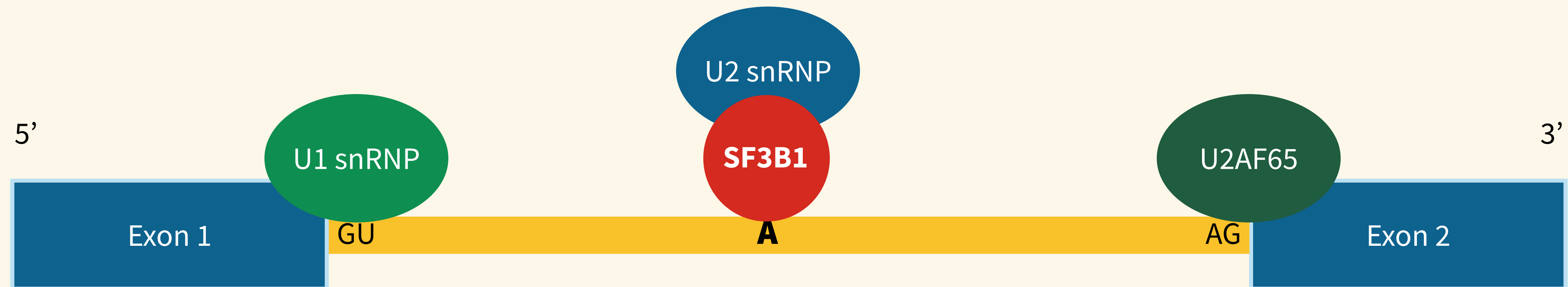
U1 small nuclear RNP attaches to 5' splice donor site

Spliceosome complex



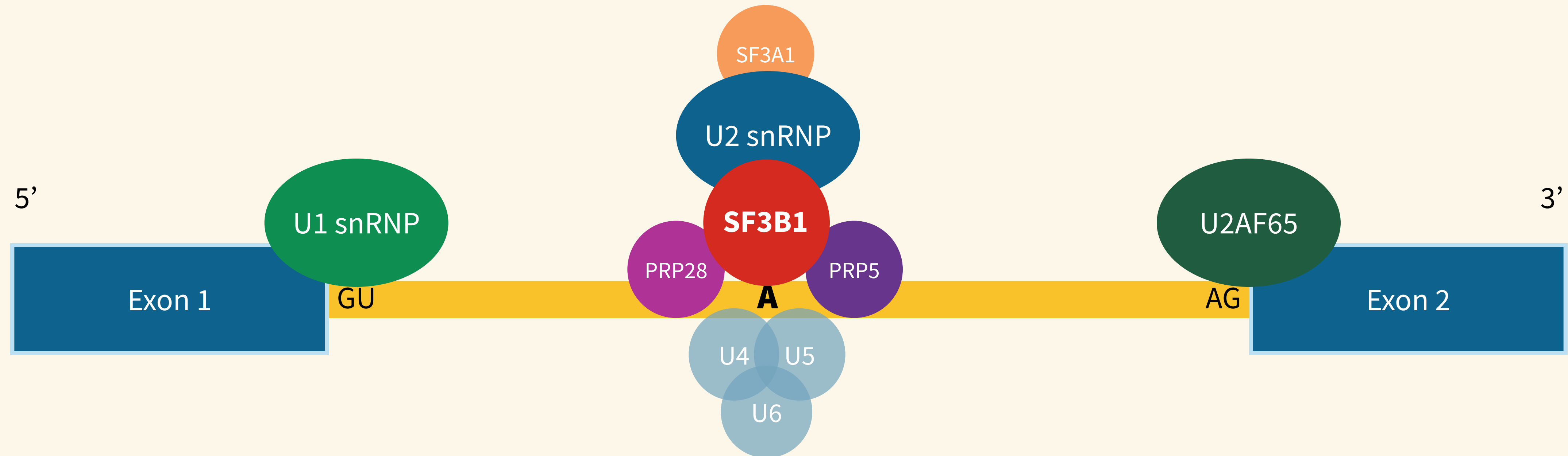
U2AF65 attaches to 3' splice acceptor site

Spliceosome complex



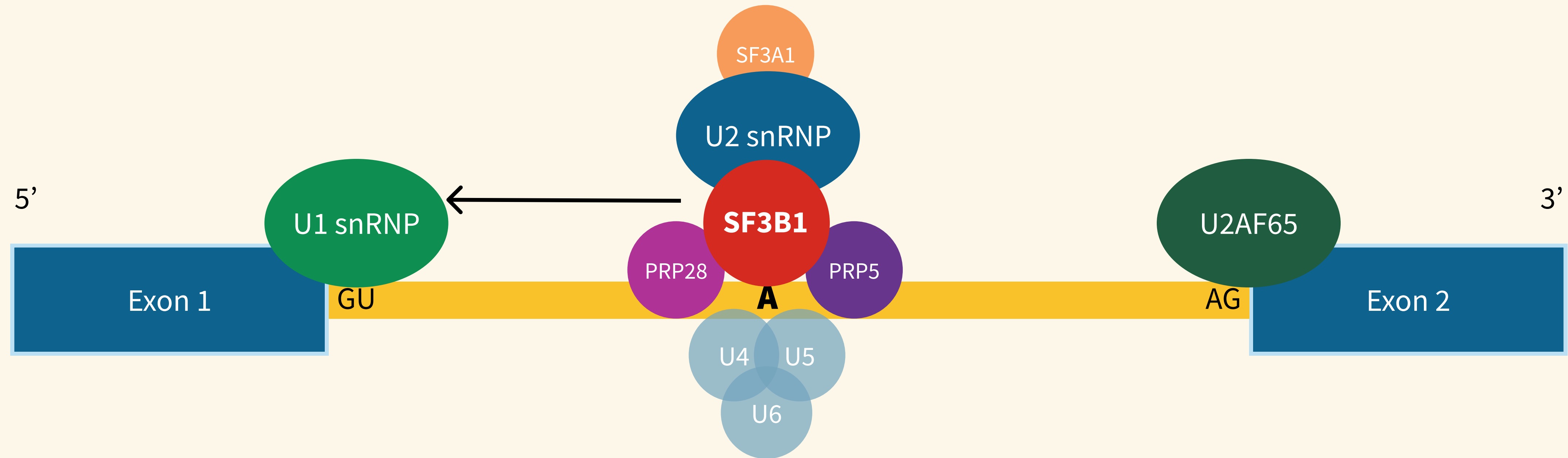
U2 snRNP containing **SF3B1** attaches to the branch point adenine

Spliceosome complex



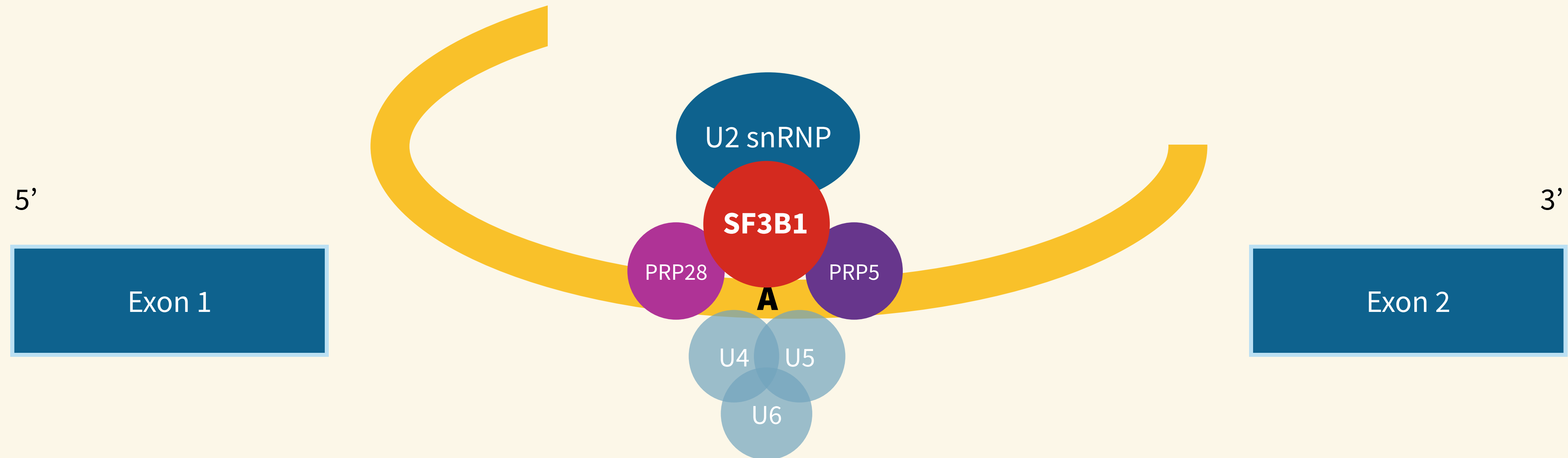
Facilitates recruitment of more proteins to form the spliceosome complex

Spliceosome complex



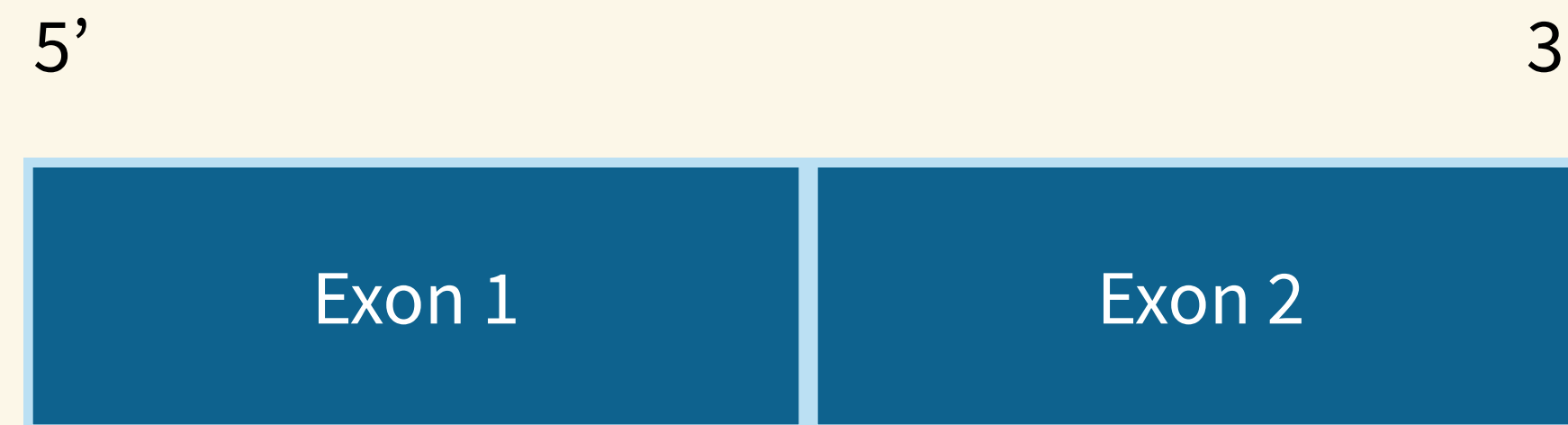
Spliceosome complex attacks 5' splice site

Spliceosome complex



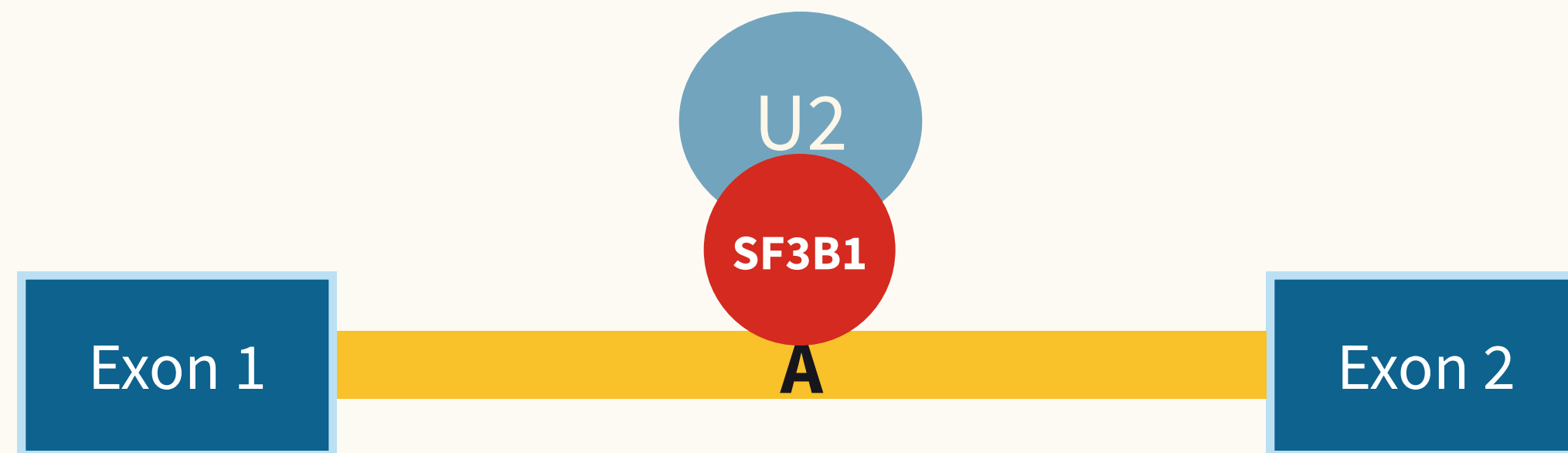
Lariat is formed and intron excised

Spliceosome complex



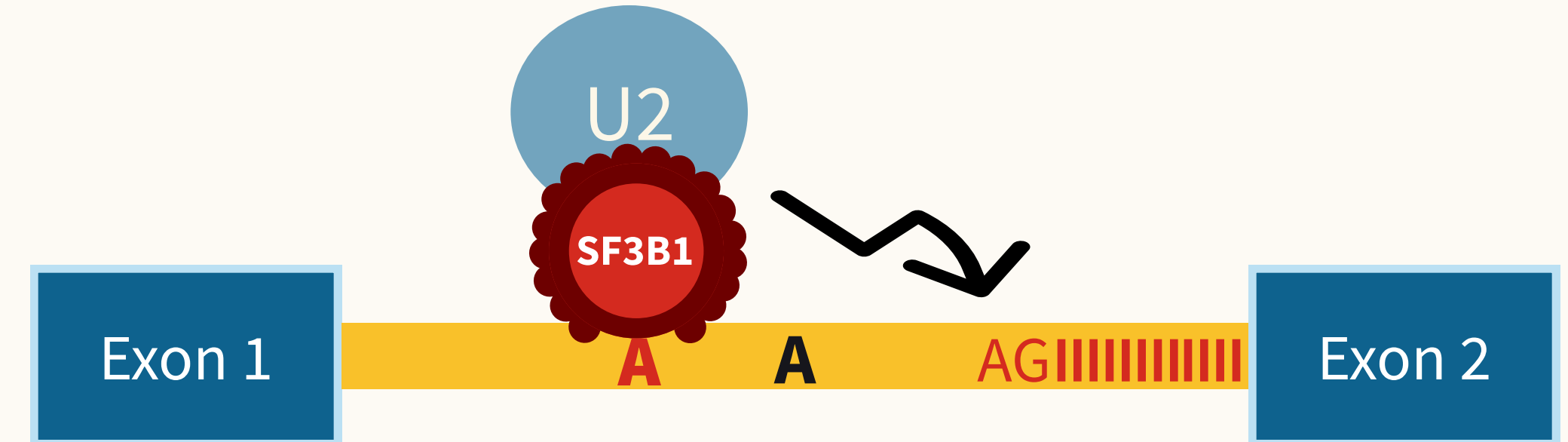
Exons are spliced

1 Function



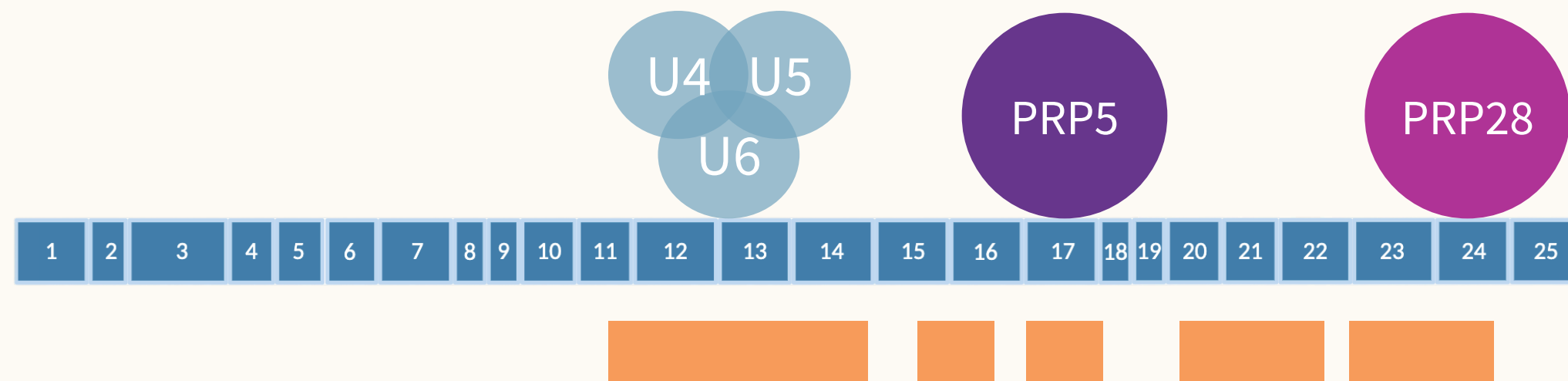
Core component of U2 snRNP for Branch Point Recognition

1 Aberration



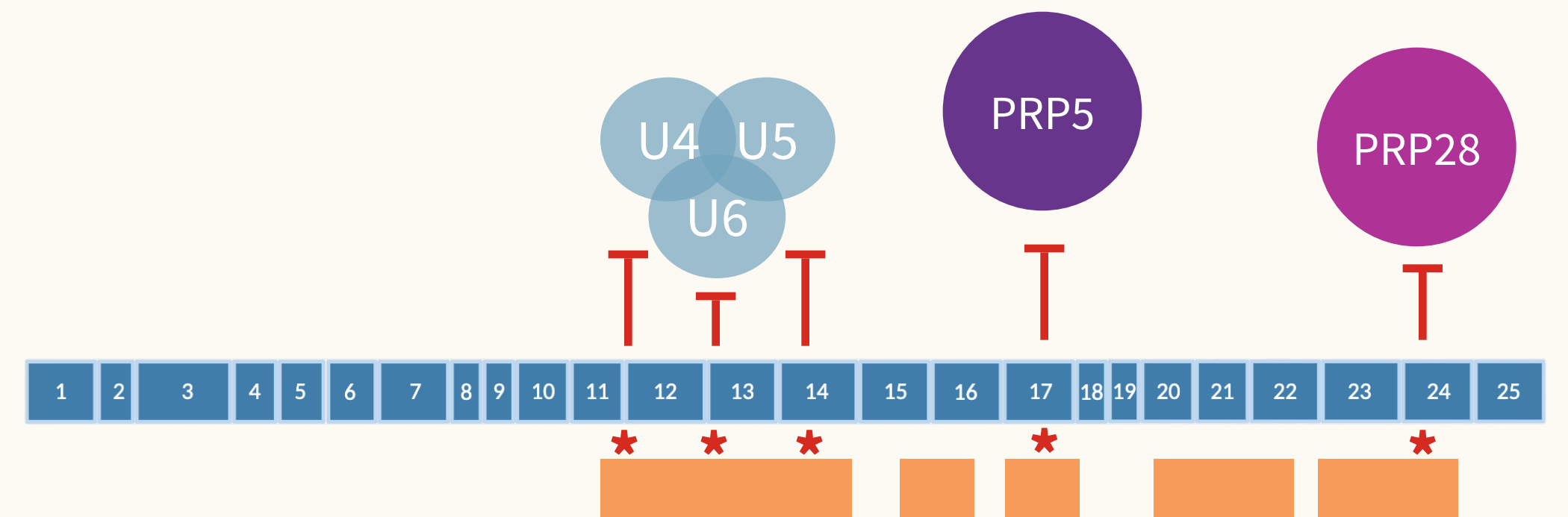
Neomorphic gain of function variants lead to aberrant branch point and 3' splice site recognition

2 Function



HEAT repeats provide scaffolding for spliceosome components

2 Aberration

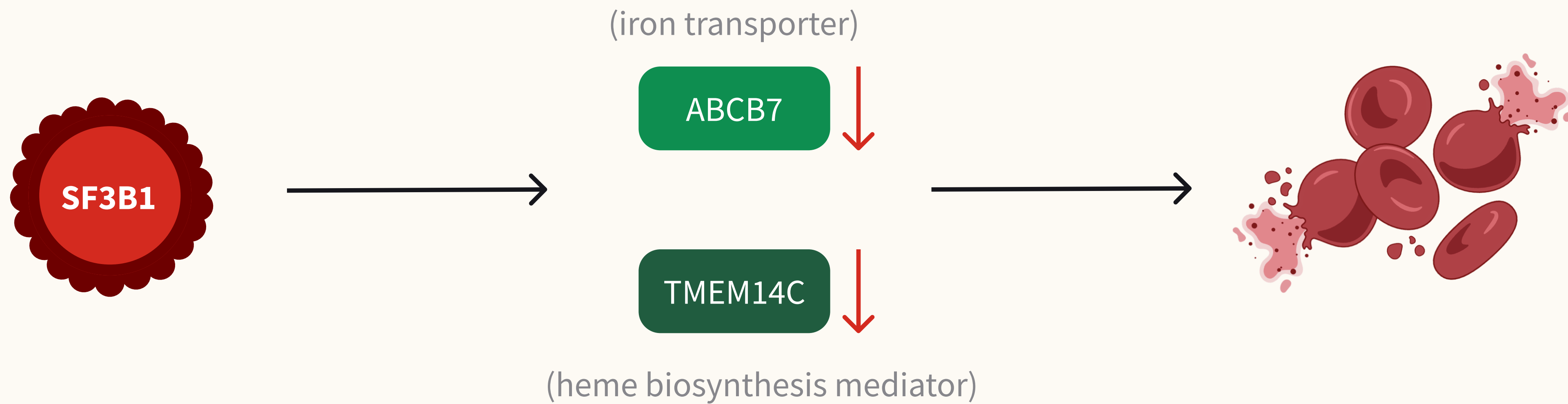


Missense variants affect binding of spliceosome components

Nonsense mediated decay

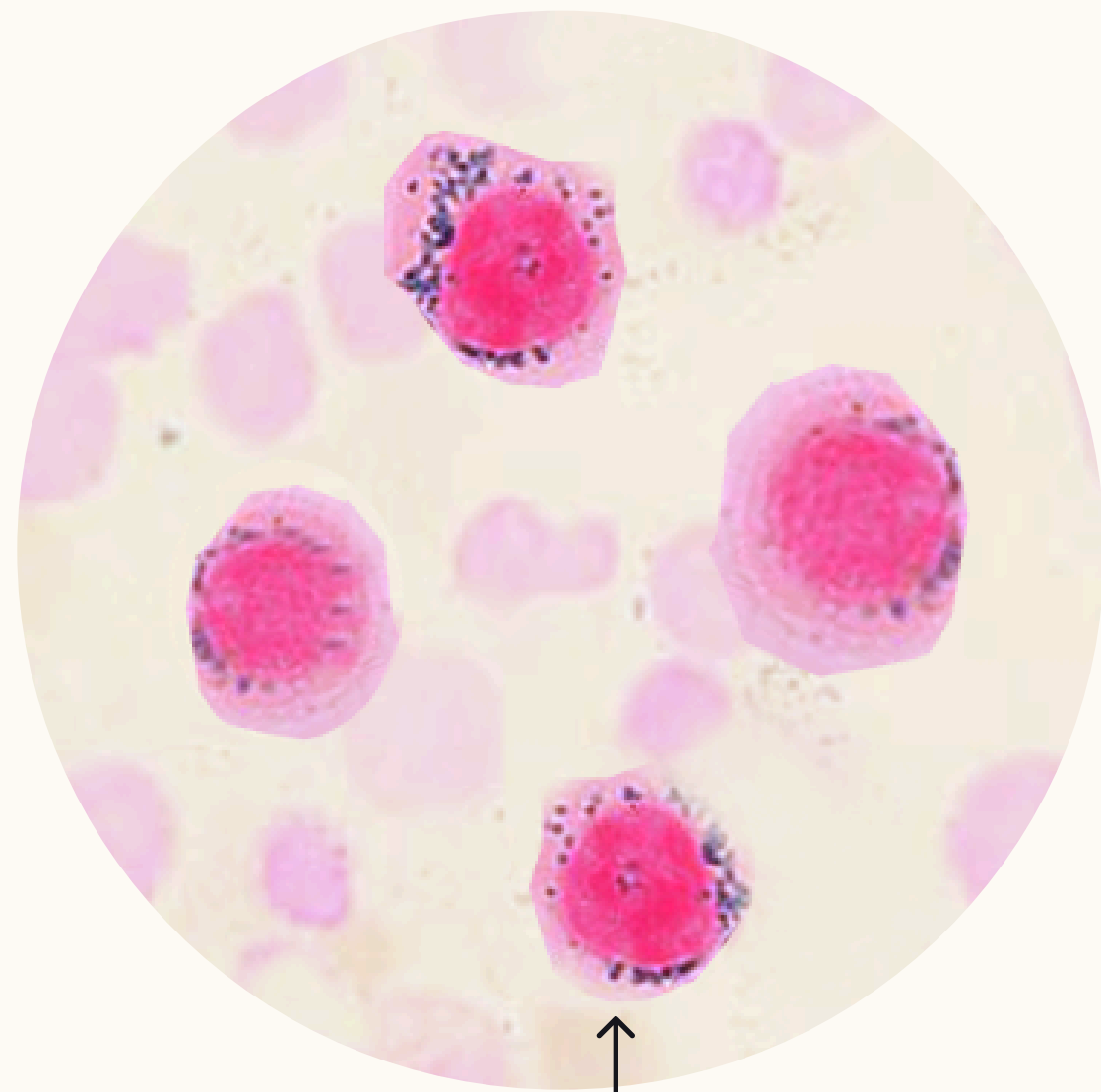


Nonsense mediated decay



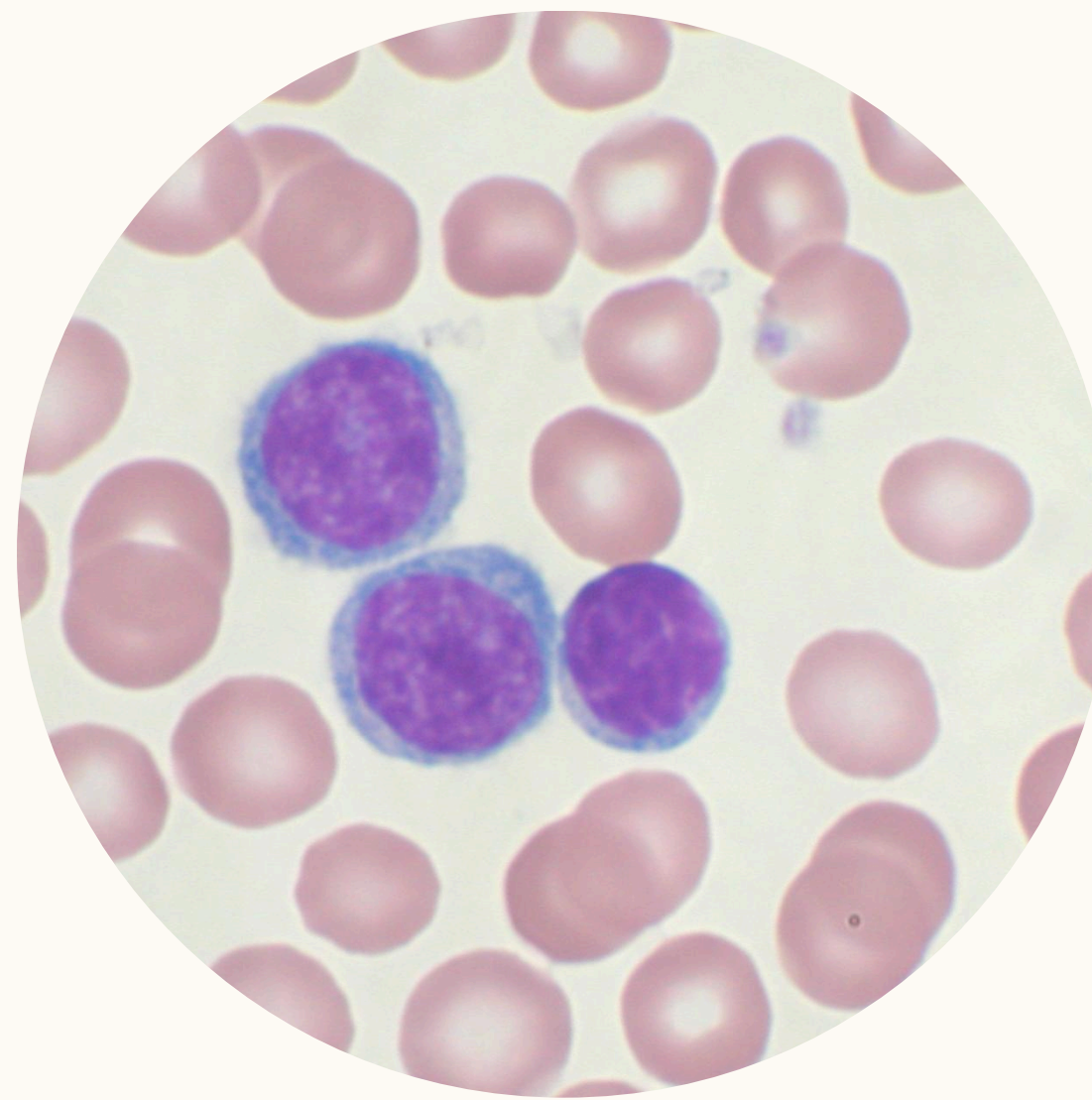
Tumor spectrum

Myelodysplastic syndromes

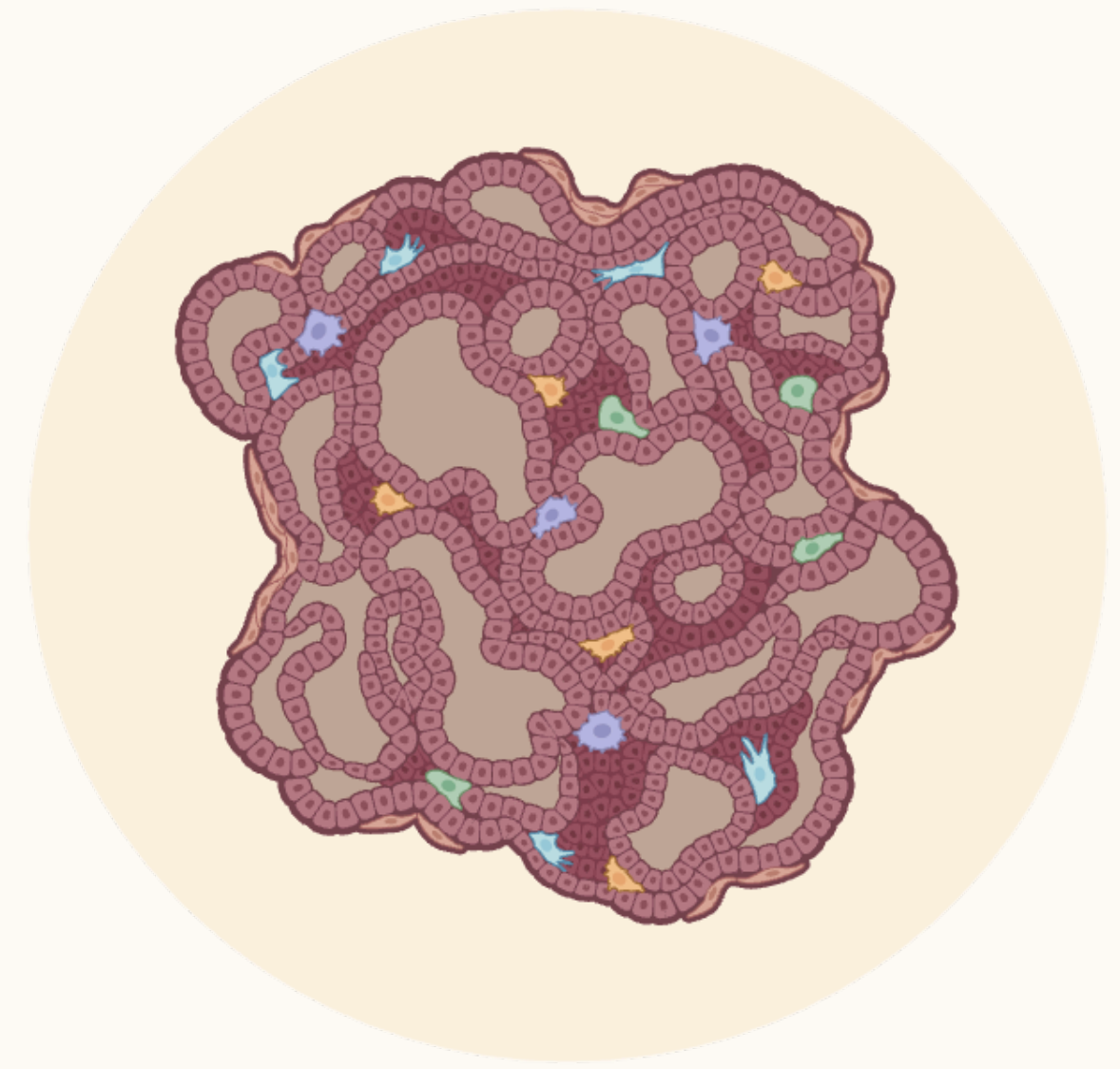


ring sideroblast

Chronic lymphocytic leukemia



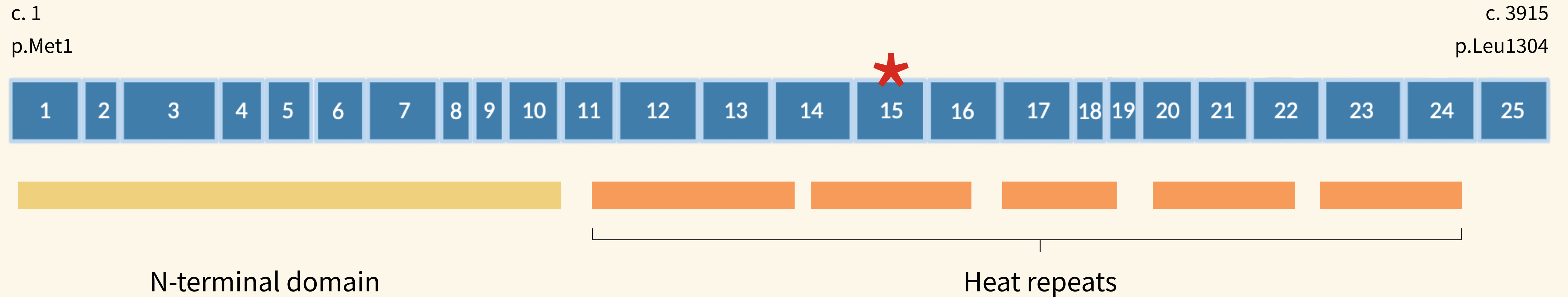
Solid tumors



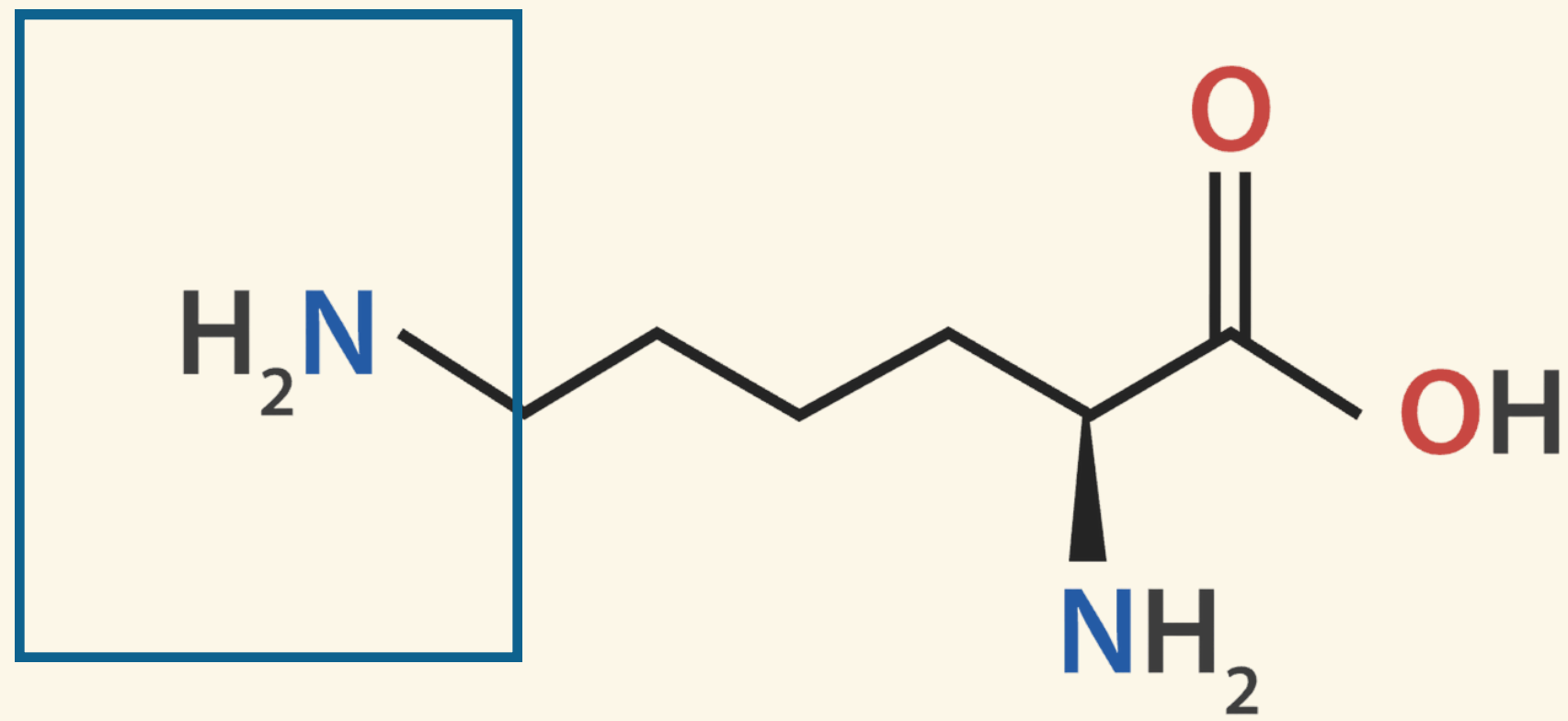
Variant information

VARIANT INFORMATION

SF3B1:c.2098A>G p.(Lys700Glu) VAF: 18%



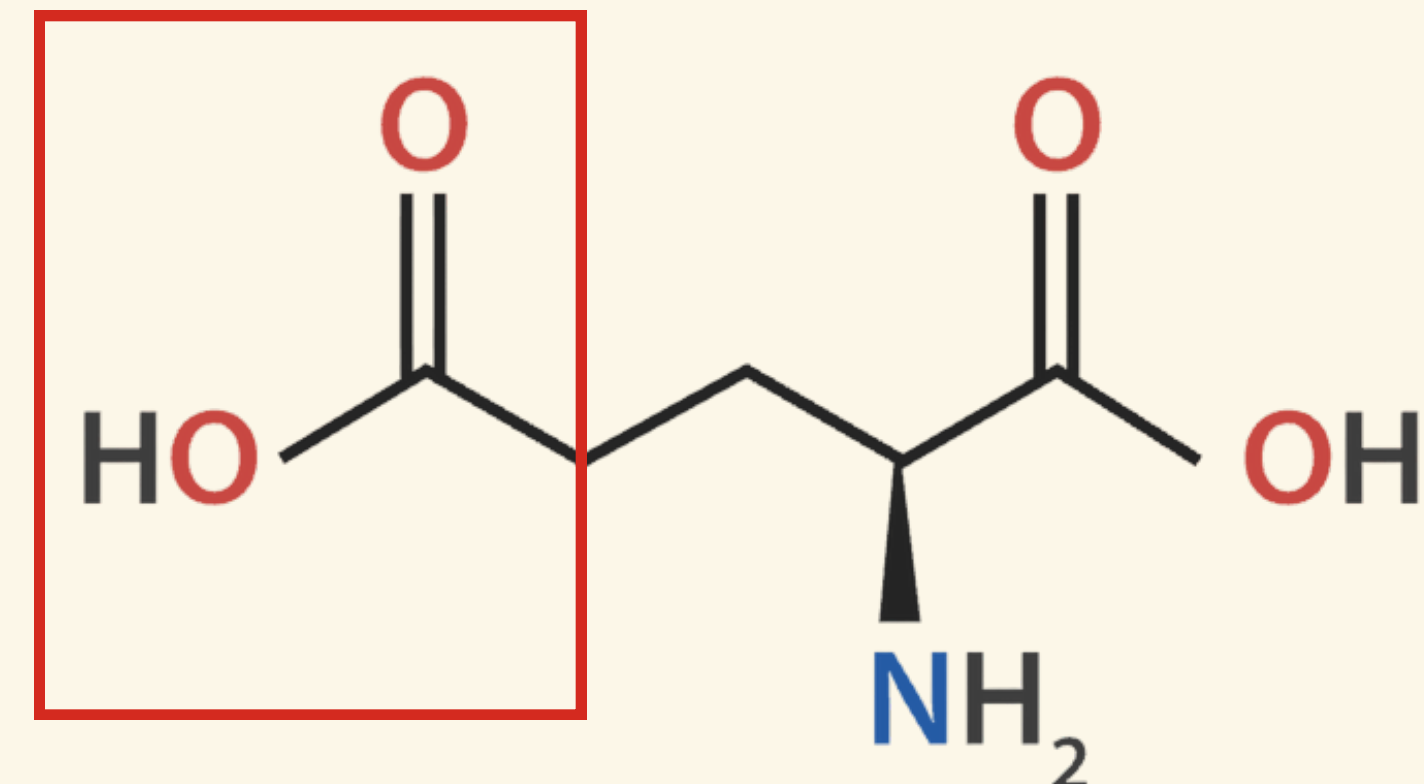
SF3B1:c.2098A>G p.(Lys700Glu)



Lysine

● Positively charged

● Basic



Glutamic acid

● Negatively charged

● Acidic

Code application

● SF3B1:C.2098A>G P.(LYS700GLU)

Population database

Evidence

GnomAD v4.1.1

Total allele count: 72

Total allele frequency: 0.00004489 (0.004489%)

Can not apply **OP4** as allele frequency 0.004489%>0.001%*

Computational data

Alphamissense score: 0.9986

Method	Score	Points
AlphaMissense	0.9986	+4 ?

OP1

All utilized lines of computational evidence support an oncogenic effect of a variant

Evidence

OP1 +1

VUS +1

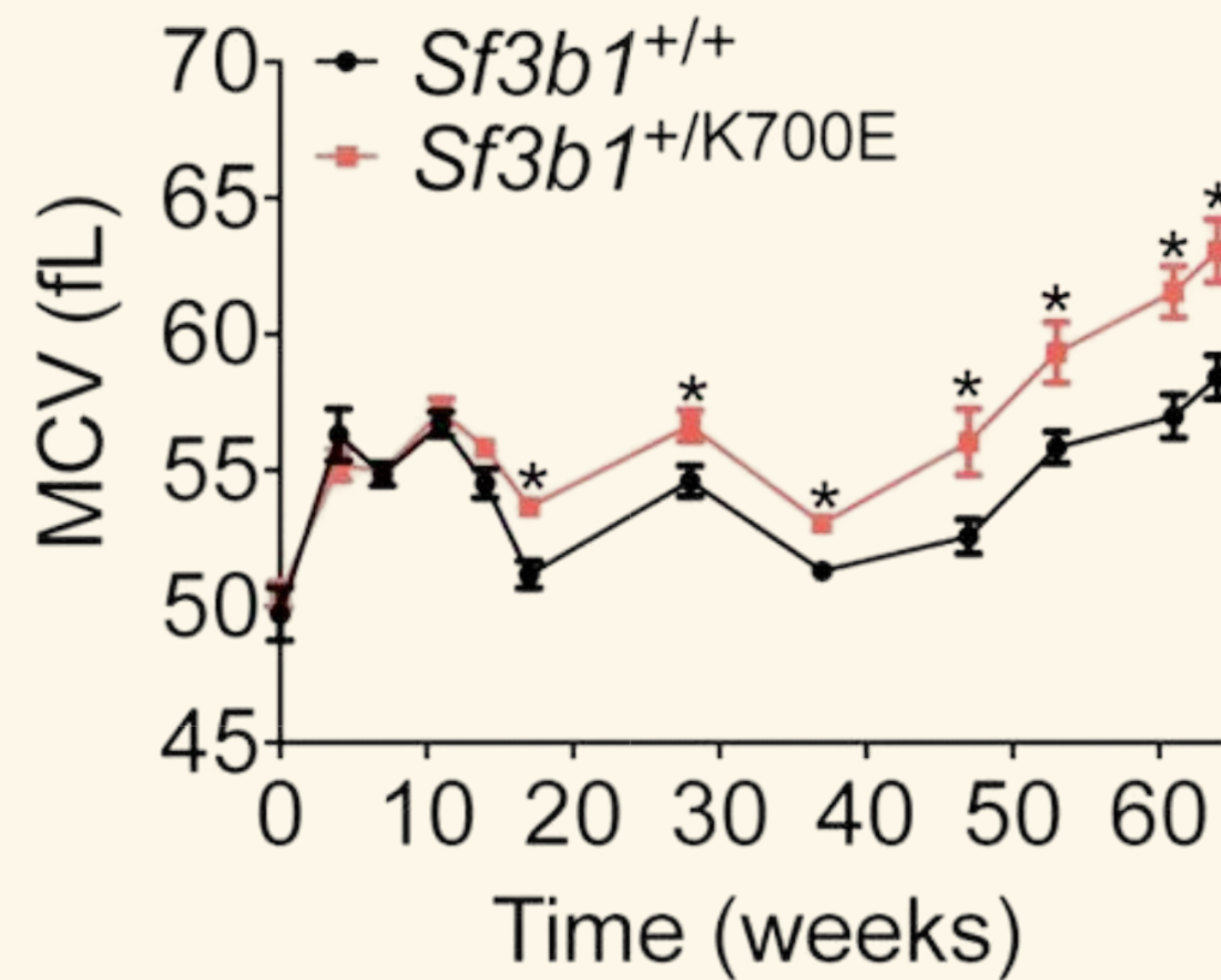
SF3B1:C.2098A>G P.(LYS700GLU)



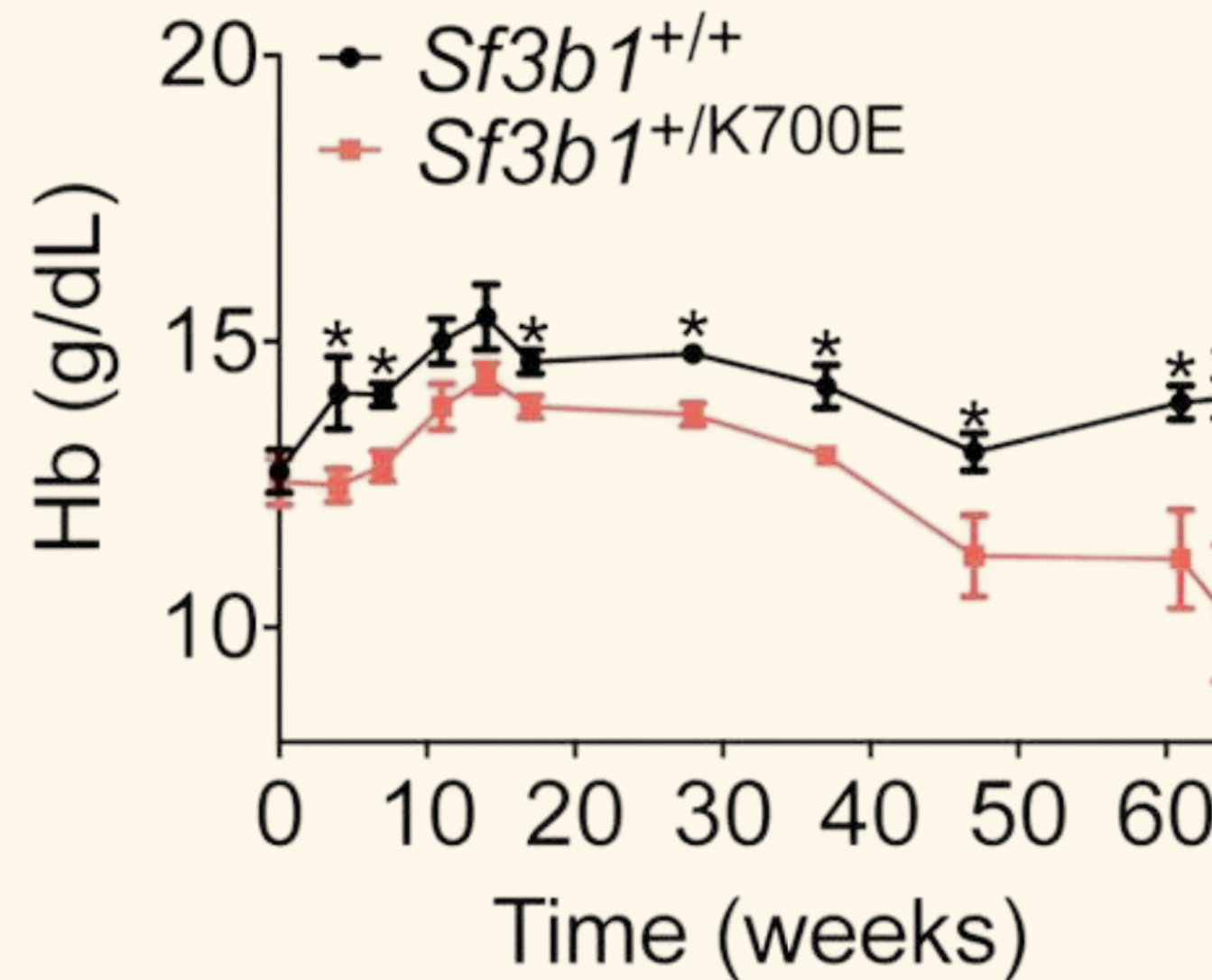
Functional data PMID: 27622333

Evidence

OP1 +1



Increased mean corpuscular volume



Decreased haemoglobin

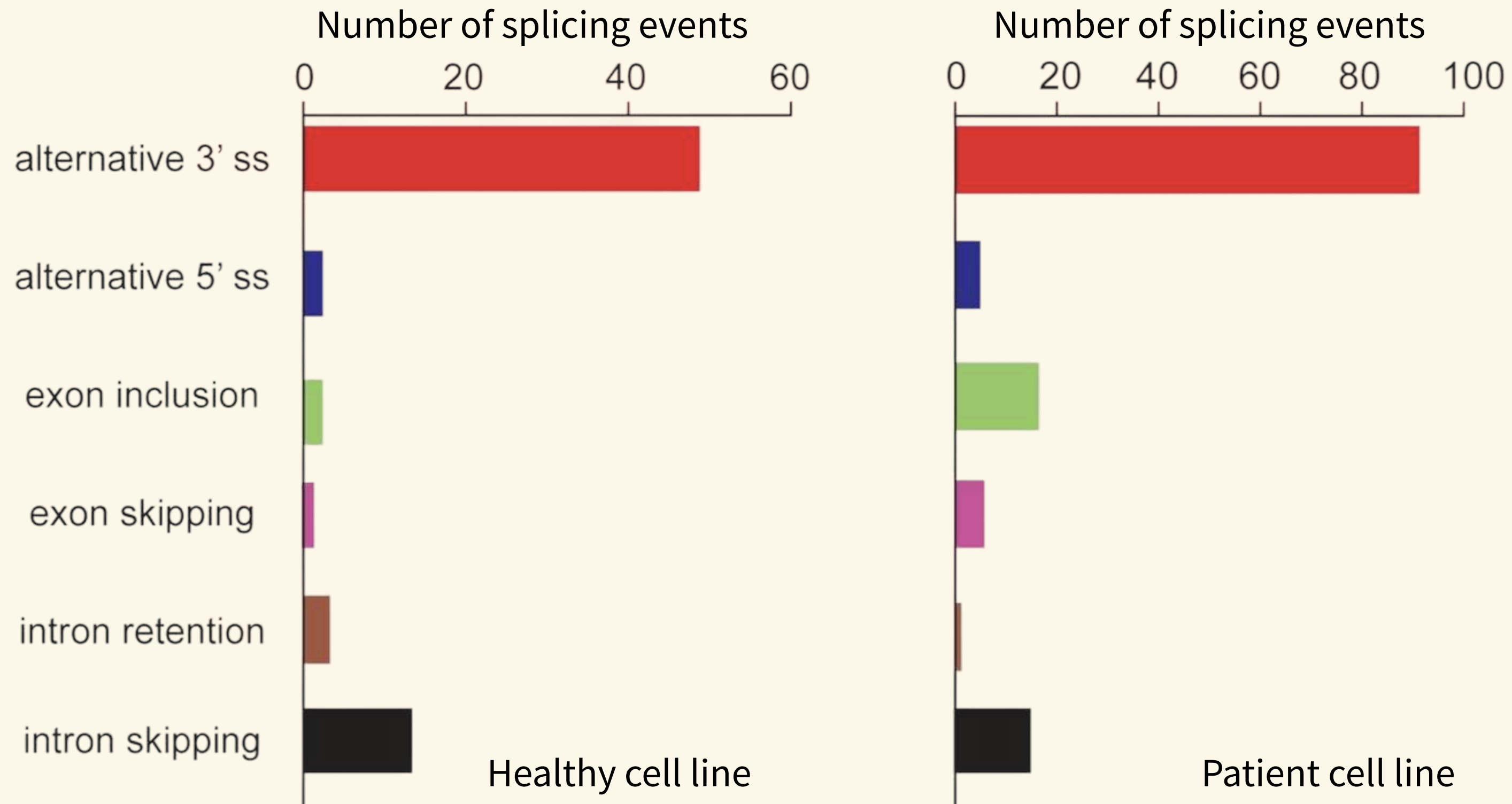
VUS

+1

SF3B1:C.2098A>G P.(LYS700GLU)



Functional data PMID: 27622333



Evidence

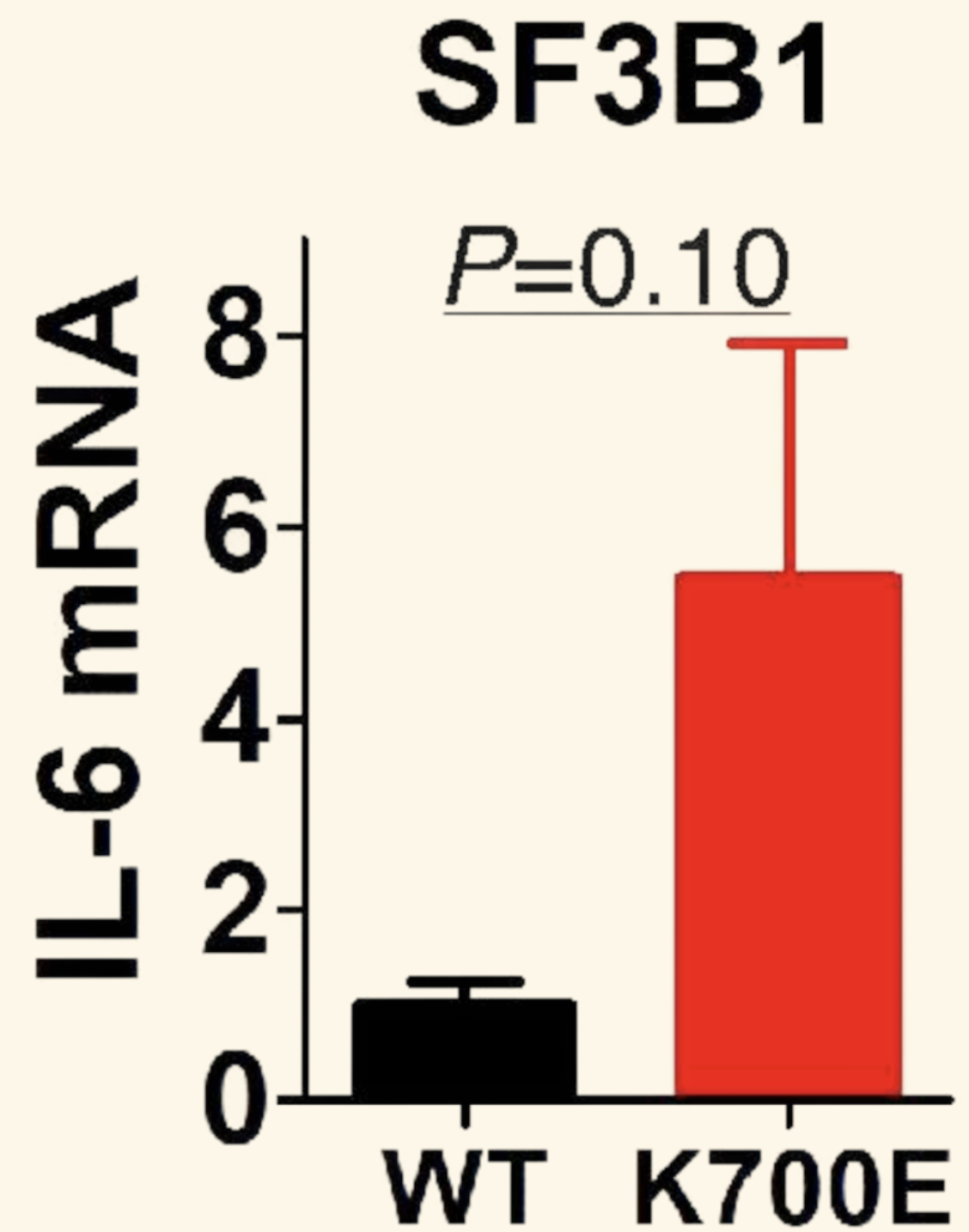
OP1 +1

VUS +1

● SF3B1:C.2098A>G P.(LYS700GLU)



Functional data PMID: 30846499



Inflammatory cytokine quantification (cancer hallmark)

Evidence

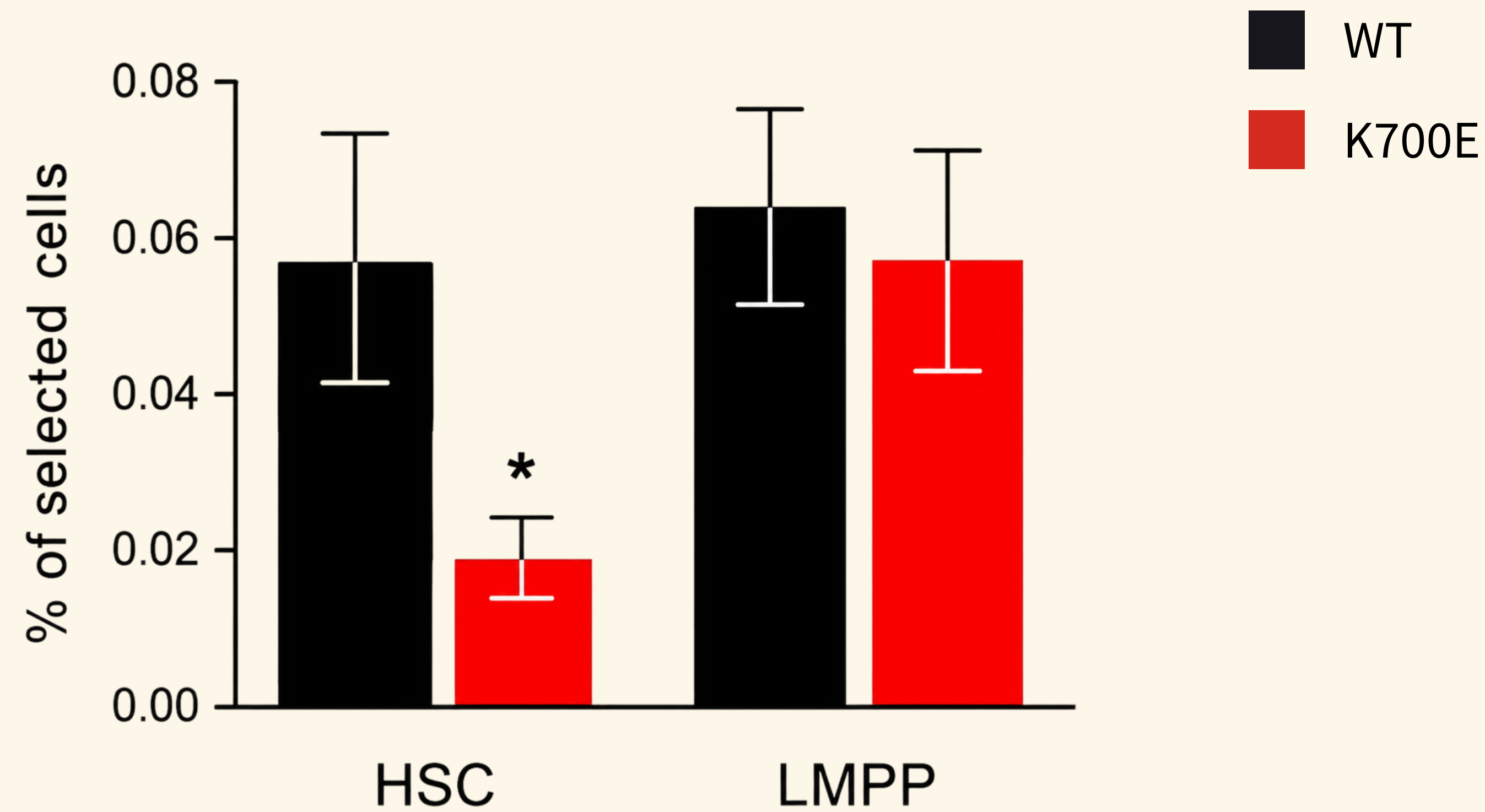
OP1 +1

VUS +1

SF3B1:C.2098A>G P.(LYS700GLU)



Functional data PMID: 27604819



Hematopoietic stem cell vs Lympho-myeloid primed progenitor cell quantification

Evidence

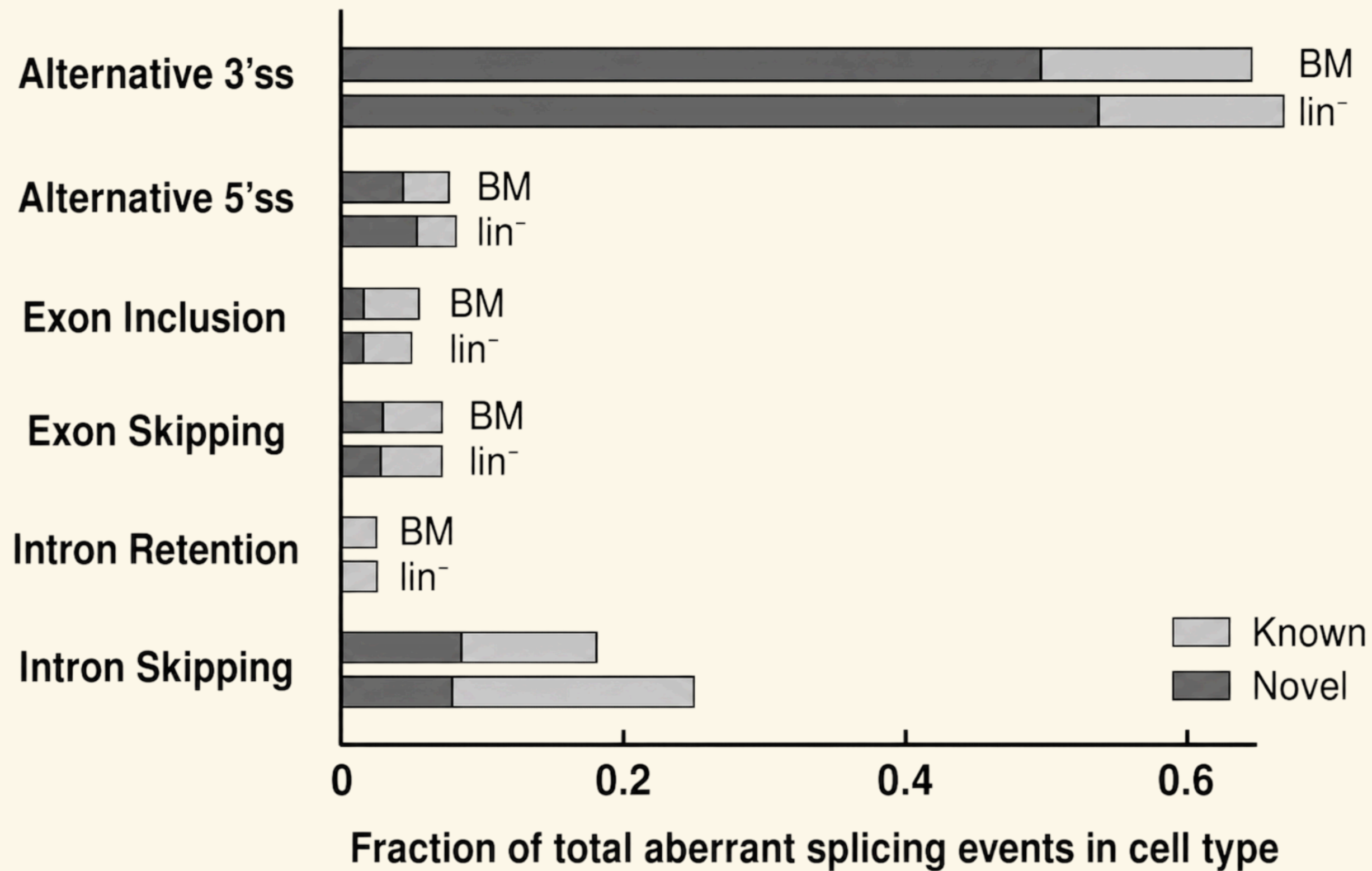
OP1 +1

VUS +1

SF3B1:C.2098A>G P.(LYS700GLU)



Functional data PMID: 27604819

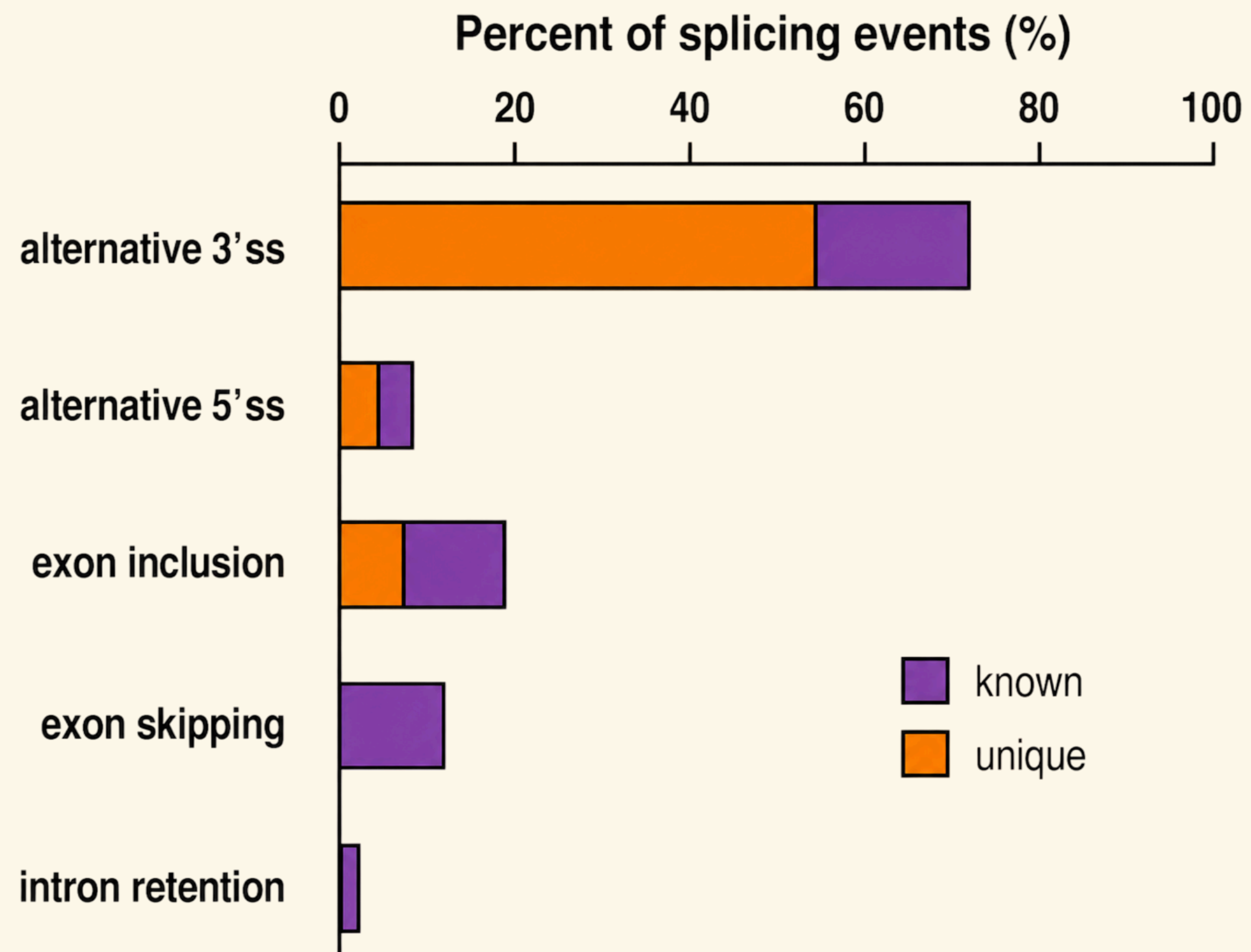


Evidence

OP1 +1

VUS +1

Functional data [PMID: 26565915](#)

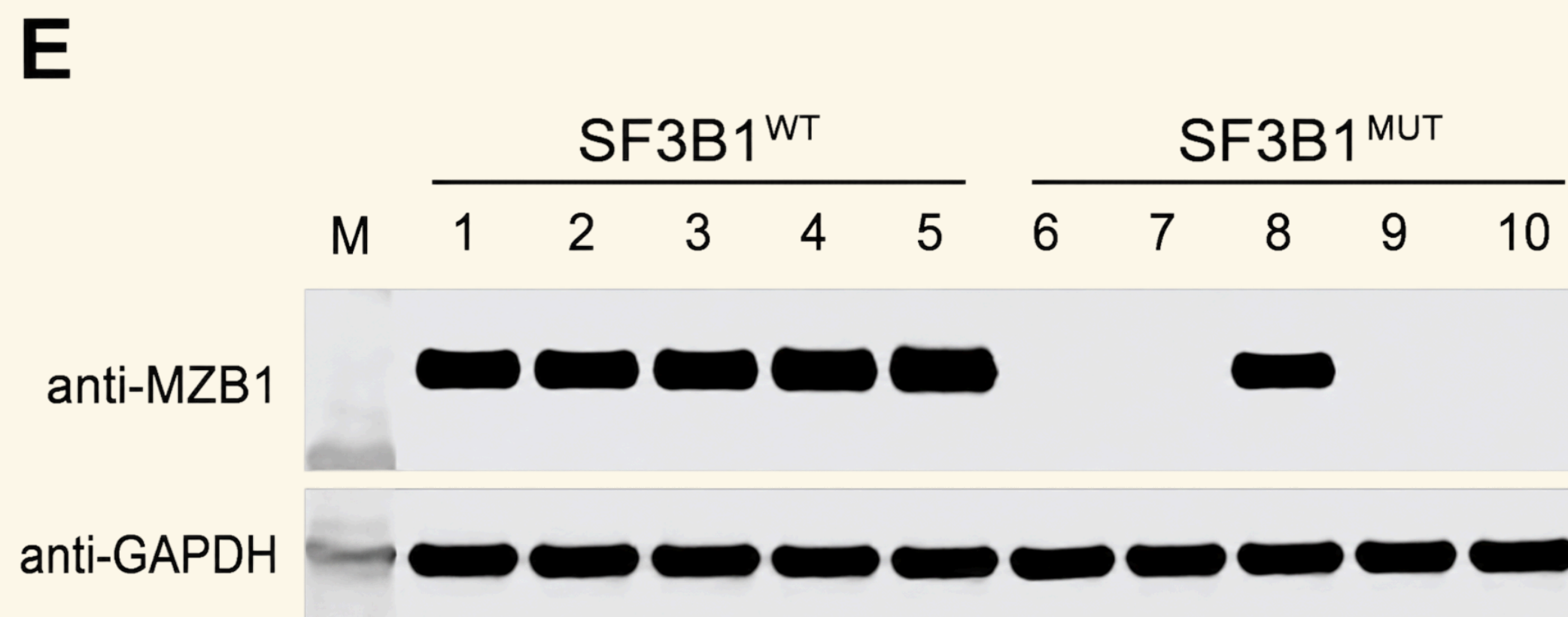


Evidence

OP1 +1

VUS +1

Functional data [PMID: 26565915](#)



Western blotting indicating loss of MZB protein due to NMD

OS2

Well-established in vitro or in vivo functional studies supportive of an oncogenic effect of the variant

Evidence

OP1	+1
OS2	+4

VUS +5

Cancer hotspot data

Variants [†]	↕	Q-value	↕	Samples [†]
E		1.52e-126		59

Variant	Count
E	57
K	1
R	1

OS3

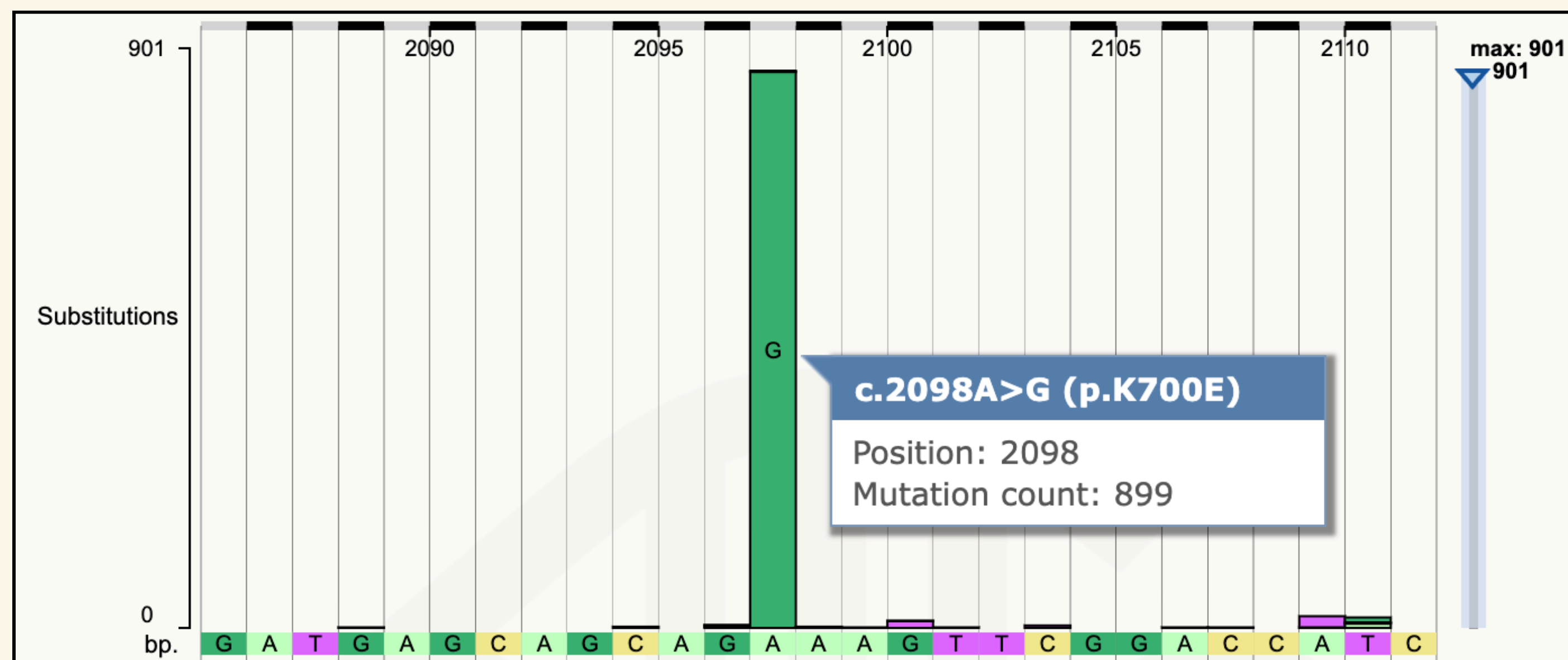
Located in one of the hotspots with > 50 samples with a somatic variant at the same AA position, and the same amino acid change count in > 10 samples.

Evidence

OP1	+1
OS2	+4
OS3	+4

Likely +9
oncogenic

Predictive data



No codes applicable

Evidence

OP1	+1
OS2	+4
OS3	+4

Likely +9
oncogenic

SF3B1: c.2098A>G p.(Lys700Glu)

**Likely
oncogenic**

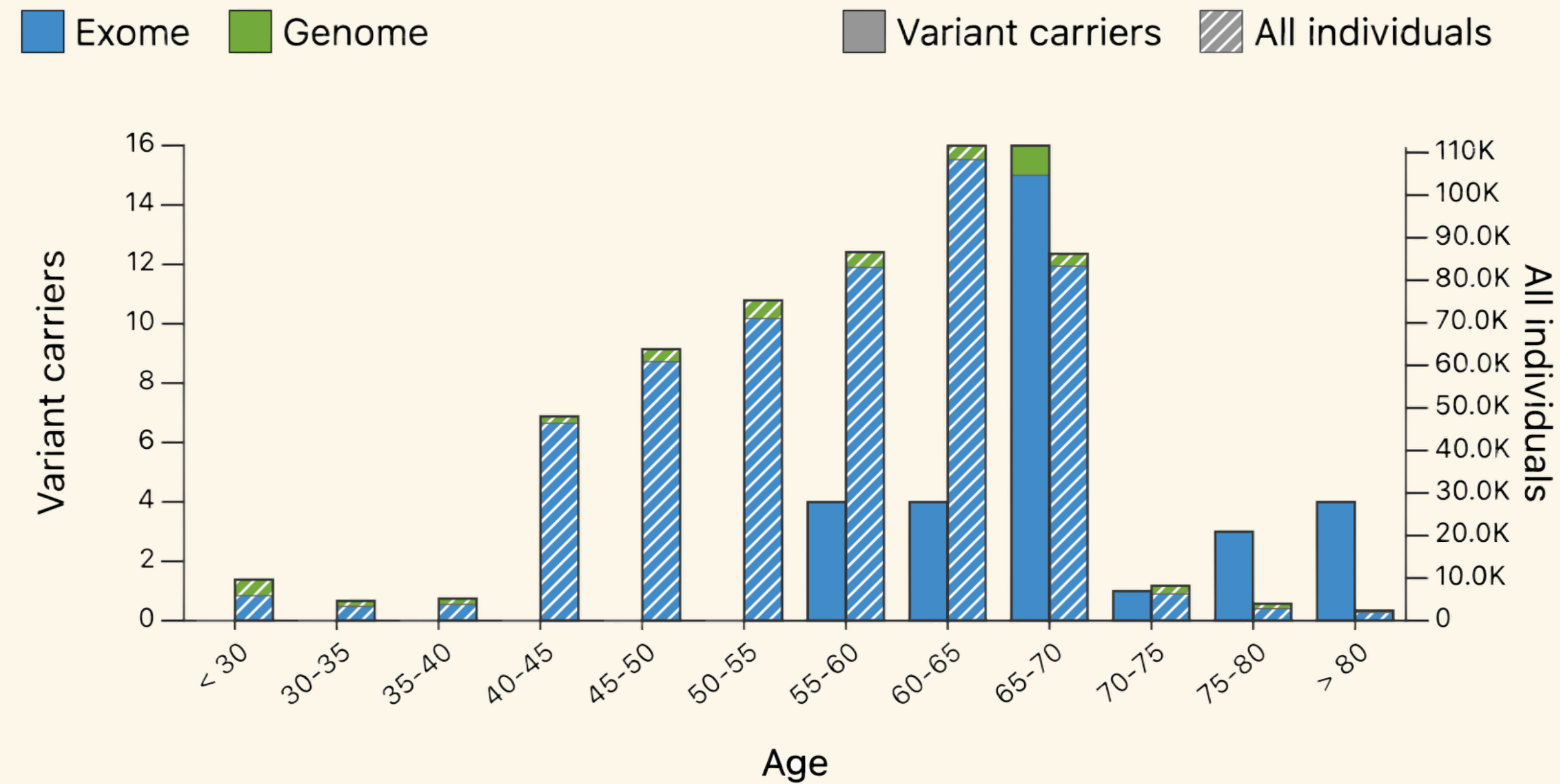
Evidence

OP1	+1
OS2	+4
OS3	+4

**Likely
oncogenic** +9

Population database GnomAD v4.1.1

Age Distribution



Evidence

OP1	+1
OS2	+4
OS3	+4
OP4	+1

Oncogenic +10

Can possibly apply **OP4** even though allele frequency **0.004489% > 0.001%** as the allele is observed for the first time in age range **55-60**.

● POSSIBLE MODIFIED CLASSIFICATION

SF3B1: c.2098A>G p.(Lys700Glu)

Oncogenic*

Evidence

OP1	+1
OS2	+4
OS3	+4
OP4	+1

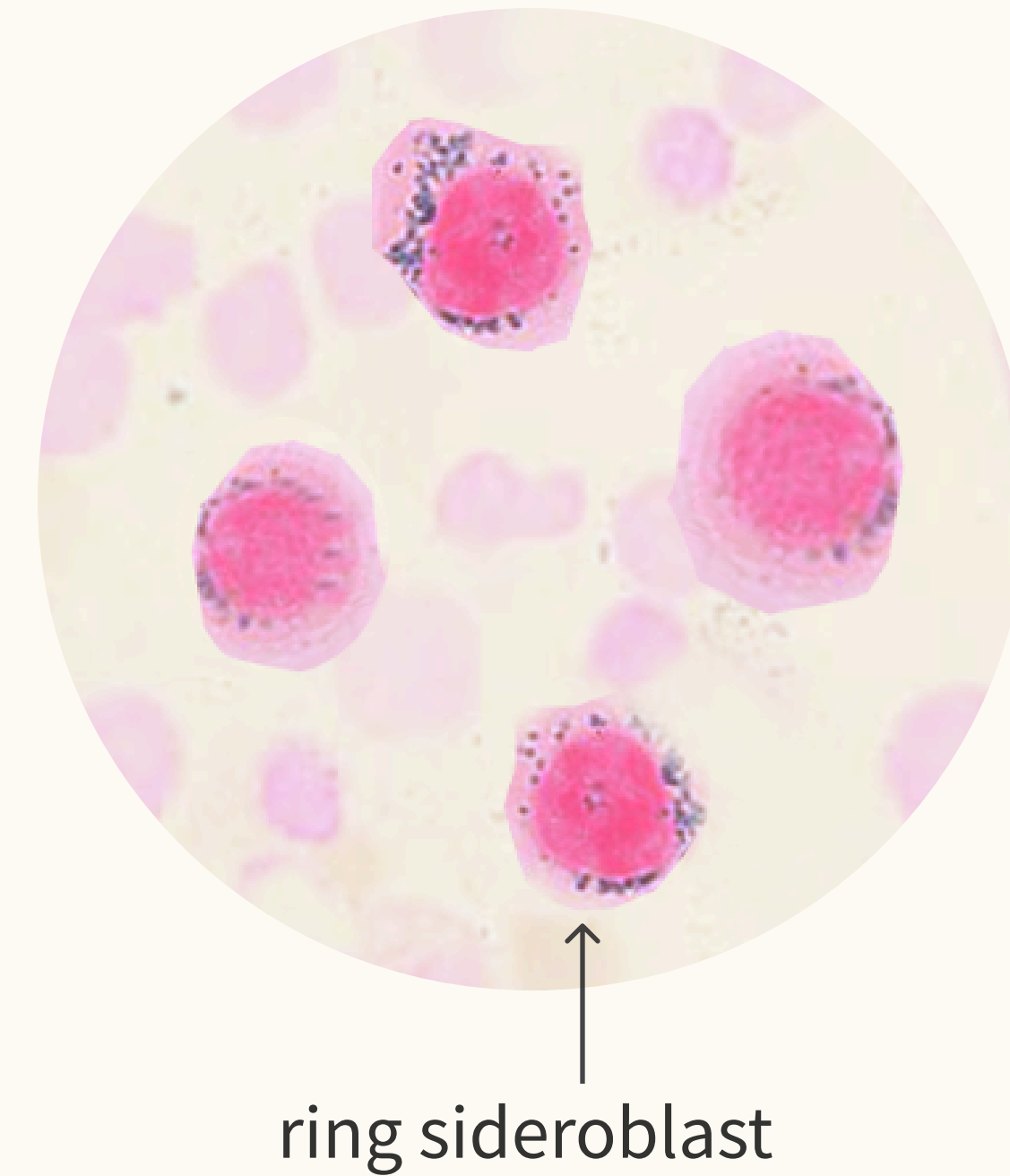
Oncogenic +10

*Variant review meeting

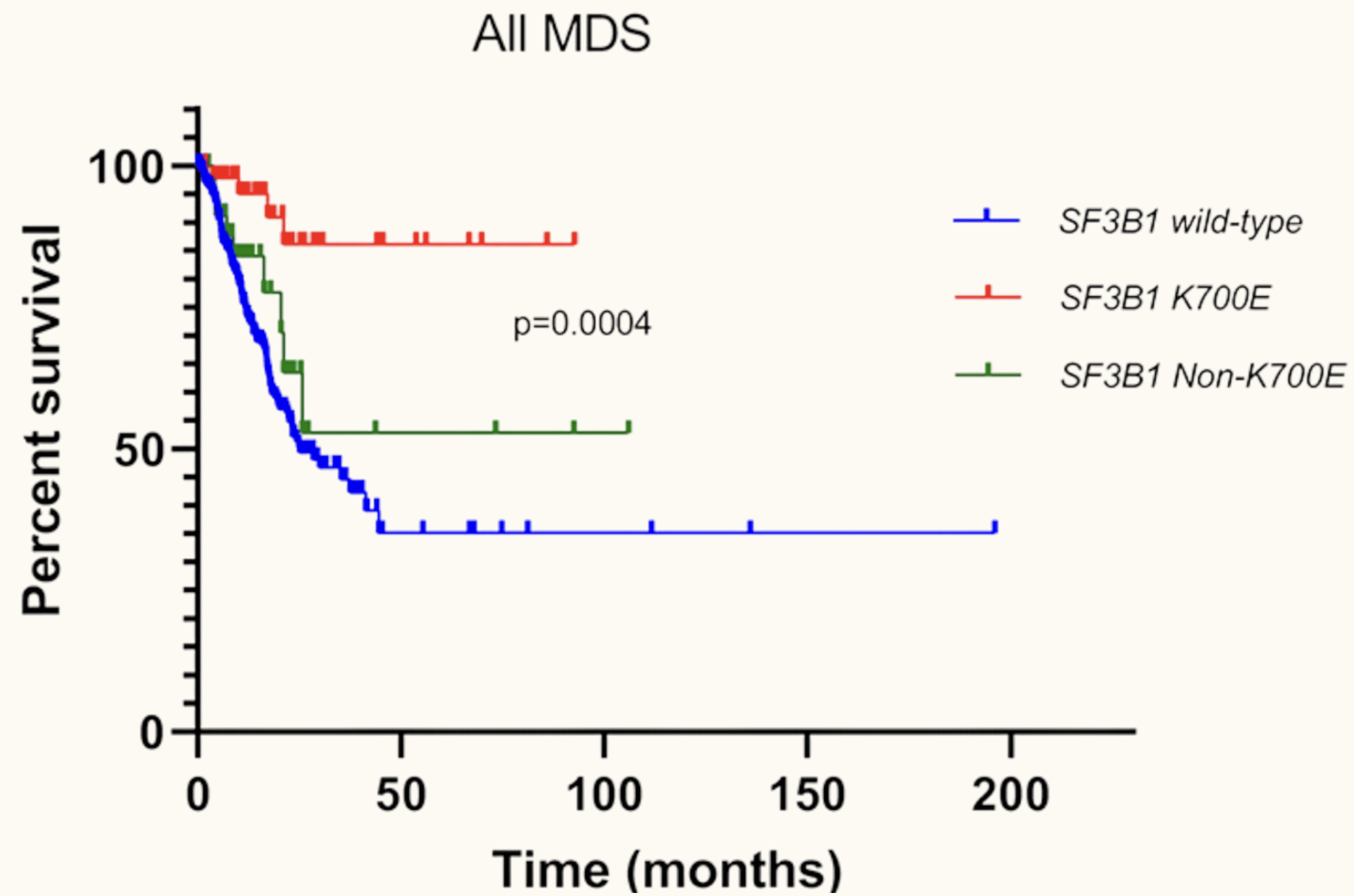
Variant implications

1 Diagnostic

**“Diagnostic of MDS with ring sideroblasts
in the presence of >5% ring sideroblasts”**

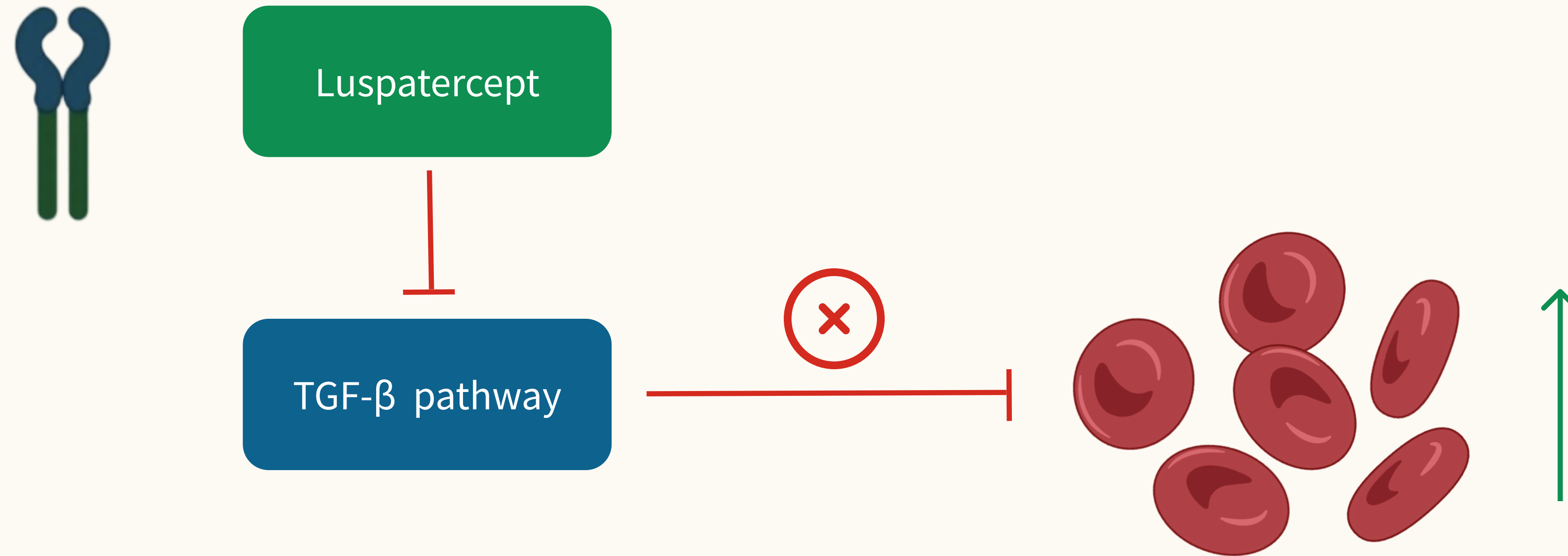


2 Prognostic

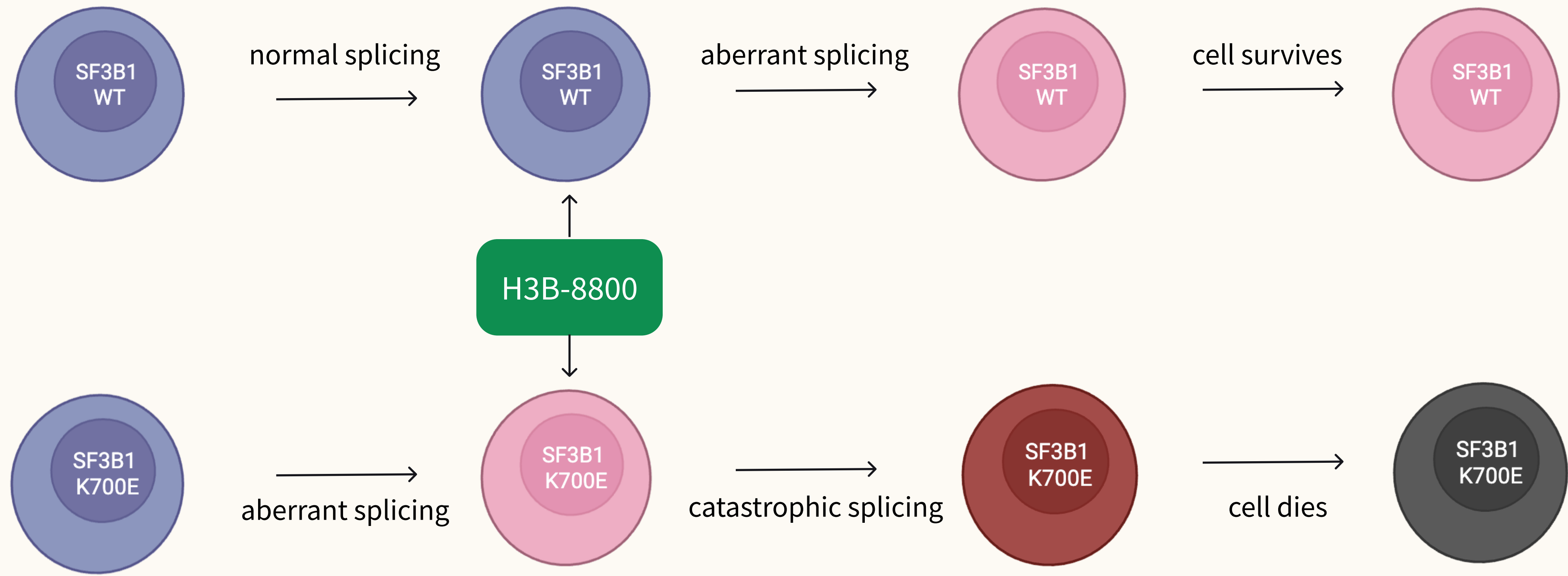


“Associated with better prognostic outcome and higher survival rates”

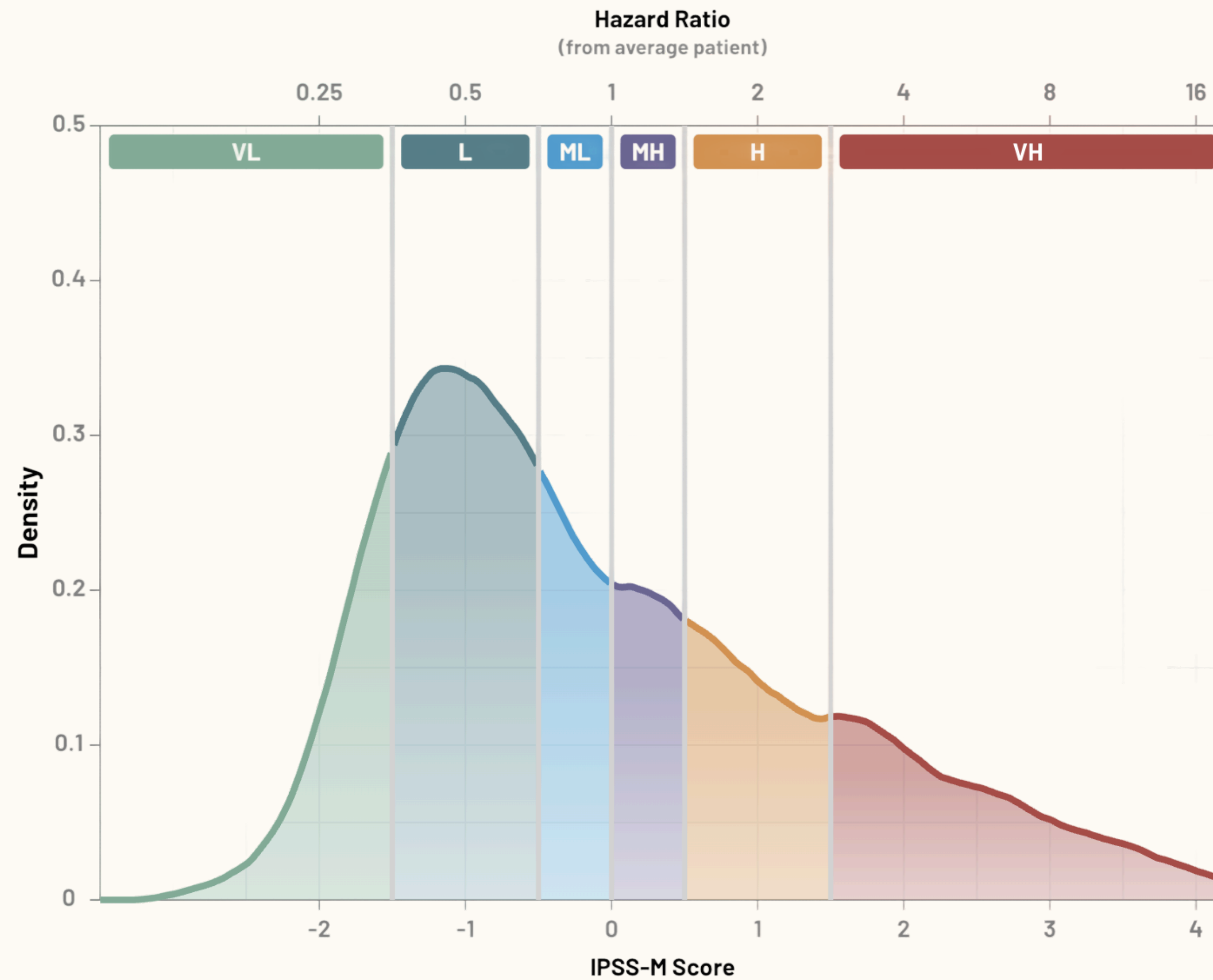
3 Therapeutic- Luspatercept (FDA approved)



3 Therapeutic- H3B-8800 (Phase 1 Clinical trial)



IPSS-M risk calculator



- Very Low | 14%
- Low | 33%
- Moderate Low | 11%
- Moderate High | 11%
- High | 14%
- Very High | 17%

*Hazard ratio for risk of AML-t or death from the average patient.

Bernard E, Tuechler H, Greenberg PL, et al, The Molecular International Prognosis Scoring System (IPSS-M) for risk stratification in myelodysplastic syndromes. *New Eng J Med Evidence*, 1(7). [doi:10.1056/evidoa2200008](https://doi.org/10.1056/evidoa2200008). Study supported by the MDS Foundation.

Questions

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