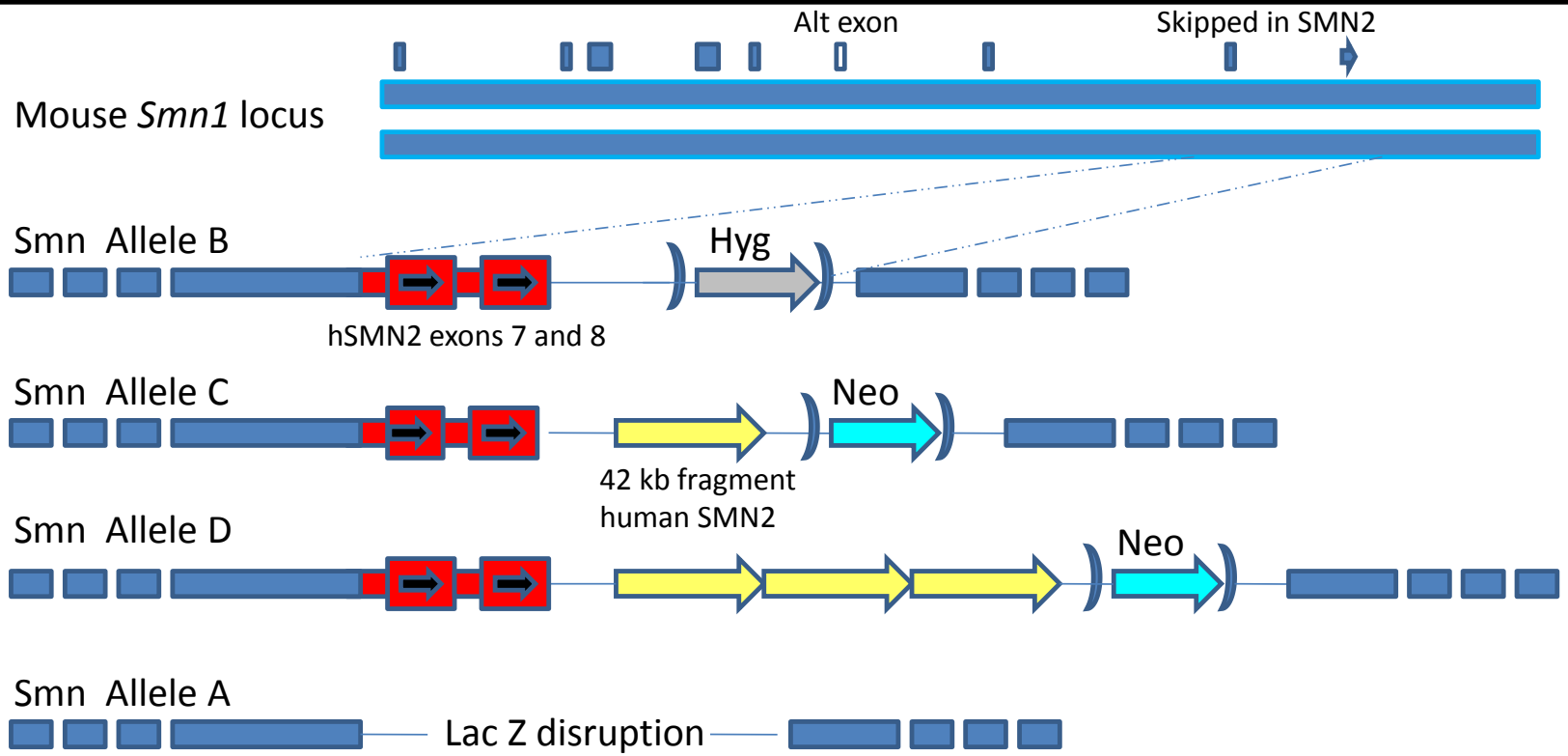
The SMA Foundation Allelic Series Mice: The Need for a Model of Mild SMA

- While several SMA mouse models are in use, the majority reflect very severe disease phenotypes and die within 1-2 weeks of birth
- The SMA Foundation contracted Regeneron Pharmaceuticals to develop models for milder forms of SMA in 2006
- Following the principle that higher SMN2 copy number produces less severe SMA disease forms, Regeneron created a series of mouse lines that had different copies numbers of SMN
  - The 4 lines created were named A, B, C, and D
  - The A-D lines had 0-1 chimeric SMN copies and 0-3 SMN2 copies each
  - The C/C mouse was the least severe viable mouse and is being characterized by multiple labs
- For more information on the phenotype of the C/C and other allelic series mice, please contact researchtools@smafoundation.org

Generating Less Severe SMA Mouse Models: Varying SMN2 Gene Copy Number



- Constructs for alleles A-D were introduced into the endogenous mouse Smn1 locus
  - In Allele A, the Smn1 gene is rendered inactive via insertion of the Lac Z gene
  - In Alleles B, C and D, human SMN2 exons 7 and 8 are introduced into the mouse Smn1 gene thus producing a chimeric gene
  - Allele C and Allele D each feature 1 to 3 copies of the full length SMN2 gene
- Different combinations of the 4 different alleles were also made

Combining Lines in the SMA Foundation Allelic Series: Severity of Phenotype Depends on SMN2 Copy Number

	A (null)	B (hybrid)	C (chimeric + SMN2)	D (chimeric + 3 SMN2)	+ (normal mouse Smn)
A (null)	Embryonic lethal	Embryonic lethal	Embryonic lethal	Viable	Viable
B (chimeric)		Embryonic lethal	Embryonic lethal	Viable	Viable
C (chimeric + SMN2)			Viable	Viable	Viable
D (chimeric + 3 SMN2)				Viable	Viable

- Animal results superficially similar to cell results: most severe combinations are lethal, least severe combinations are viable

SMA Foundation Allelic Series Mice: Available from The Jackson Laboratory

Line	Hybrid SMN1 Copies	SMN2 Copies	Phenotype	Jax Stock # BL6	Jax Stock # FVB
A/A	0	0	Embryonic lethal	7963	7955
A/B	1	0	Embryonic lethal		
A/C	1	1	Embryonic lethal		
A/D	1	3	Viable		
B/B	2	0	Embryonic lethal	8453	8713
B/C	2	1	Embryonic lethal		
B/D	2	3	Viable		
C/C	2	2	Viable, necrosis	8714	8604
C/D	2	4	Viable		
D/D	2	6	Viable	9378	9391

- Mice listed with JAX stock numbers are available to order in congenic C57/Bl6 or FVBn background