

Matrix of SMN Mutations – Emily Brecher – Summer 2007

**An exon 7 point mutation in the C-terminus of SMN1 (C>T) produces SMN2 protein (self-association affected) by aberrant splicing; the result is less full-length SMN protein, thereby causing motor neuron cell death

Mutation	Exon or Intron	Mutation Type	SMA Type	Number of SMN2 Genes	<i>In Vitro & In Vivo</i> Functions	Result/Effects/Hypotheses/Conclusions
No SMN1 transcript (entire gene del) ²²	All	Gross Deletion	I, II	2		
ΔN-Terminal ^{1,2}		Partial Deletion			Affects multifunctional abilities of SMN protein (particularly pre-mRNA splicing) ¹	Blocks spliceosome regeneration/recycling <i>in vitro</i> ¹
5'ivs7bpdel(-13) ^{4,15}	Non-Coding	Deletion				
c.5C>G (A2G, 38C>8) ^{23, 28, 36, 37}	E1	Missense	II, III	0 - ?	In mice lacking the SMN2 gene, a mutant SMN A2G transgene is insufficient to rescue embryonic lethality; however, in mice with some SMN2, an A2G transgene can delay motor neuron cell death, restore gems, induce sprouting, reduce muscle weakness and increase lifespan (i.e. produces a milder phenotype) ³⁷ SMN A2G binds to full length SMN with less affinity than native SMN but greater affinity than SMNΔ ³⁷ Binding to Sm protein is reduced even though the A2G mutation is not located in the previously-identified Sm binding domain ³⁷	Mutant oligomers are unstable and bind poorly to components necessary for SMN function ³⁷ Low levels of full length SMN may be required for the A2G transgene to produce partially active higher order SMN complexes ³⁷ SMN levels are an important determinant of SMA onset and severity (even when dealing with mutant alleles) ³⁷
c.22_23insA (22dupA) ^{38, 39}	E1	Insertion Frameshift	I or II			
c.43C>T (p.Q15X, 76/78C>T) ^{22, 26}	E1	Nonsense	I, III	2, 3		
c.81_82+1insG (c.81dupG, p.Q27fsX30, Q27insG) ^{30, 31, 36, 37}	E1	Insertion Frameshift	II			
c.88G>A (p.D30N) ²²	E2a	Missense	II	2	Interaction of SMN and SIP1, and oligomerization of SMN were undisturbed ²²	Mild mutation since only have partial loss of SMN1 protein function ²² Tudor domain may not interact directly with SIP1; rather, this mutation may destabilize the SMN-SIP1 interaction or interfere with the interaction of other components and the SMN N-terminus ²² Mutations in exon 2a do not interfere with SMN's ability to bind with Sm or SIP1, therefore binding to other SMN interacting proteins may be affected ²²

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c.90_91insT (124insT, c.91dupT, p.S31fsX33) ^{23, 26, 36, 37}	E2a	Insertion Frameshift	I, II	2		
c.131A>T (p.D44V) ²²	E2a	Missense	IIIb	1	Interaction of SMN and SIP1, and oligomerization of SMN were undisturbed ²²	Mild mutation since only have partial loss of SMN1 protein function ²² Tudor domain may not interact directly with SIP1; rather, this mutation may destabilize the SMN-SIP1 interaction or interfere with the interaction of other components and the SMN N-terminus ²² Mutations in exon 2a do not interfere with SMN's ability to bind with Sm or SIP1, therefore binding to other SMN interacting proteins may be affected ²²
c.198_214del17 (p.P66fsX71) ³⁶	E2b	Deletion Frameshift (Premature Stop)	I	2		Interferes with SIP1 binding and self-association ³⁶
c.208_209insGTGT (241-242ins4, p.P70fsX73) ^{23, 26, 36, 37}	E2b	Insertion Frameshift	IIIa	3		
c.275G>C (p.W92S) ²¹ *at N-terminal of SMN Tudor domain	E3	Missense	I	3	Severely reduced interaction of the Tudor domain with fundamental components of nuclear RNA-protein complexes (Smb protein and fibrillarlin) in <i>in vitro</i> protein binding assays ²¹	Impaired critical function of SMN (inability to interact with target proteins involved in snRNP domain assembly and 2'-O-methylation of ribosomal RNA) ²¹
c.281T>G (p.V94G) ^{36, 42}	E3	Missense	II	3		Mutation is located in a loop before a β 1 strand so it does not appear to affect Tudor domain tertiary structure; however, it may alter positioning of a functional SMN domain ³⁶
c.283G>C (p.G95R) ^{21, 22}	E3	Missense	III	1	Reduced (not abolished) SMN binding to Sm proteins ²² However, interaction of SMN and the SMN-interacting protein Germin2 (also known as SIP1) is undisturbed ²²	Suggests that Tudor domain is essential binding site of SMN to Sm proteins ²²
c.305G>A (p.W102X) ^{2, 35, 36}	E3	Nonsense (Premature Stop)	II, III	2	Aminoglycosides prevent SMN exon 3 skipping in cultured cells ³⁵ Fibroblasts contain many nuclear structures containing gems (SMN protein) ³⁵	Loss of exon 3 produces shortened transcripts that are translated normally (i.e. get expected shortened protein) ³⁵ Protein lacking exon 3-encoded region may play a role in forming the nuclear SMN protein complex; this may result in a milder phenotype irrespective of a low SMN2 copy number ³⁵ SMN Tudor domain is not necessary for gem formation ³⁵

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c.314_317dupACGG (p.G106fsX119) ³⁶	E3	Insertion Frameshift (Premature Stop)	III	4		
c.332C>G (p.A111G) ^{21, 22}	E3	Missense	I, II	2	Reduced (not abolished) SMN binding to Sm proteins ²² However, interaction of SMN and SIP1 (which binds to N-terminus of SMN) and oligomerization of SMN were undisturbed ²²	Suggests that Tudor domain is essential binding site of SMN to Sm proteins ²²
p.I116F ²	E3	Missense	I		Affects highly conserved region of SMN Tudor domain ²	
c.399_402delAGAG (p.R133fsX148, 430/432-4bp AGAG del, 430del4) ^{2, 3, 4, 11, 23, 32, 33, 36}	E3	Deletion Frameshift Premature Stop	I, II, III, IV, no symptoms	1, 2, 3		Homozygosity for this mutation is less deleterious than heterozygosity combined with a complete SMN1 deletion ³³ Mutated SMN1 transcript may regulate/increase levels of full length SMN2 transcript ³³ SMN transcription may be influenced by SMN2 copy number as well as other yet to be identified regulatory or epigenetic factors ³³
c.400G>A (p.E134K) ^{1, 3, 7, 8, 20, 22, 23, 36}	E3	Missense	I, II	2	Sm protein chaperone activity inhibited (involves deficit in snRNP core assembly) ¹ SMN with E134K does not bind to the <i>in vitro</i> translated Smb protein ²⁴ SMN protein with E134K associates only slightly with the <i>in vitro</i> translated fibrillarin ²⁵	Failure to bind with Sm proteins (C-terminus; strands β4 & β5) and gamins but protein still self-associates (i.e. gem formation) ¹ Allows inappropriate SMA-causing Sm protein oligomerization and prevents desirable complexes ¹
439_433delGAAGT (p.136fsX138, 425del5, 471-472del5) ^{2, 3, 4, 12, 21, 23, 35, 36}	E3	Deletion Frameshift Premature Stop	I	1, 2		
p.Q136E ²	E3	Missense	I		Affects highly conserved region of SMN Tudor domain ²	
c.509_510delGT (542delGT, p.S170fsX179) ^{23, 28, 30, 36, 37}	E4	Deletion Frameshift	I, II, III			
c.558delA (591delA, p.K186fsX213) ^{23, 26, 36, 37}	E4	Deletion Frameshift	II	2		
c.585dupT (c.585_586insT, 618insT, p.P196fsX256) ^{4, 19, 20, 23, 30, 36, 37}	E4	Insertion Frameshift	I	1, 2		
IVS4_IVS6del (6.4kb Alu-mediated Δ) ^{23, 26}	I4-I6 E5, E6	Gross Deletion	I			
c.683T>A (p.L228X) ^{38, 39}	E5	Nonsense	I or II			

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hSMN Δ5-Δ6 (del ex5-6, c.627+?_835+?del, p.P210_M278del) ^{26, 36}	E5, E6	Gross Deletion	I, II, IIIb	2, 3		
c.734C>T (767C>T, p.P245L) ^{3, 16, 23, 30, 36, 37, 42}	E6	Missense	III			
c.740dupC (773insC-CCACCT>CCACCCT, 740_741insC, p.P247fsX256) ^{30, 32, 36, 37}	E6	Insertion Frameshift Premature Stop	III			
c.770_780dupCTGATGCTTTG (c.768_778dup11, 800ins11, 813ins/dup11, p.G261fsX269) ^{3, 4, 13, 23, 30, 36, 37}	E6	Insertion Frameshift	I, II	2, 3		Disruption of SMNT on its own is sufficient to produce a severe type I SMA phenotype ¹³
c.779T>C (p.L260S) ^{36, 42}	E6	Missense	II	2		
c.784A>G (p.S262G) ^{21, 22}	E6	Missense	III	1	Interaction of SMN and SIP1, and oligomerization of SMN were undisturbed ²²	
c.785G>T (818G>T, p.S262I) ^{3, 17, 18, 23, 26, 30, 36, 37}	E6	Missense	IIIb	1	Self-oligomerization capacity of SMN is negatively affected (mild) ^{17, 22}	
c.788T>G (p.M263R) ^{36, 42}	E6	Missense	I	2		
c.815A>G (848A>G, p.Y272C) ^{3, 5, 6, 15, 16, 22, 23, 26, 36, 37}	E6	Missense	I, II, IIIb	1, 2, 3	Reduced survival of mice infected intercerebrally with SV-SMN-Y272C ⁵ Activation of mitochondrial apoptotic pathway in NGF/dBcAMP-deprived or UV-treated co-differentiated PC12 and Rat-1 cells ⁶ Severe impairment of oligomerization <i>in vitro</i> ³⁷	Resistance to proteolytic processing ⁵ Production of proapoptotic form of SMN ⁶
c.821C>T (854C>T, p.T274I) ^{3, 17, 22, 23, 26, 34, 36}	E6	Missense	II, IIIa	1, 2	Mild impairment of oligomerization; degree of impairment correlated with SMA severity <i>in vivo</i> ³⁷	Codons 258 to 279 contain an important functional domain; disruption within this tyrosine/glycine-rich motif hinders binding to RNA binding proteins, therefore suggesting a role for SMN in RNA metabolism ¹⁷ Mild mutation since only have partial loss of SMN1 protein function ²² Homozygous deletion of exon 7 in SMN1 is not required to produce SMA ³⁴
c.823G>A (p.G275S) ^{3, 19, 23, 31, 36}	E6	Missense	III			

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hSMN ($\Delta 6$) $\Delta 7^{6, 7, 8, 9, 10}$	E6, E7	Gross Deletion			<p>Proapoptotic activity in Rat-1/McyER cells⁶</p> <p>Loss of survival function in PC12 cells deprived of trophic support and Rat-1 cells induced to die by activation of proto-oncogene c-Myc⁶</p> <p>hSMN mutants exhibit altered subcellular localization compared with endogenous SMN and transfected full-length SMN (exon 7 contains cytoplasmic targeting signal)^{6, 7}</p> <p>Neurite growth is inhibited (progressive loss of motor axons and motoneurons in the CNS of a mouse model of SMA carrying a deletion of exon 7)^{9, 10}</p> <p>However, expressing SMN$\Delta 7$ on a type I SMA genetic background alleviates the disease phenotype⁹</p>	<p>C-terminal region is critical in suppression of apoptosis by SMN⁶</p> <p>Misfolding of native full length SMN or alteration of proteins that associate with SMN⁹</p>
c.834+2T>G (c.867+2T>G, IVS6+2T>G, p.I242_M278del) ^{30, 32, 36, 37}	I6	Splice Site Deletion	I	>1		
c.835-11del7 (c.868-11del7, IVS6-18_IVS6-12delCCTTTAT, p.G279_N294del) ^{15, 23, 36, 37}	I6	Splice Site Deletion	I	1		
$\Delta 7$ - $\Delta 8^{40}$	E7, E8	Gross Deletion	?-IV			
Fusion of SMN1 Exon 8 & cBCD541 Copy Gene Exon 7 ⁴¹	E7, E8	Complex Rearrangement				
c.835G>T (868G>T, p.G279C) ^{23, 29, 36, 37}	E7	Missense	II, III			
c.836G>T (869G>T, p.279G>V) ^{3, 14, 23, 36, 37}	E7	Missense	I		Impaired oligomerization <i>in vitro</i> ³⁷	
c.888+3delAGTC (c.922+3del14, 3'ivs4bpdel(+10)?, IVS7+4_IVS7+7delAGTC, p.G279_294del) ^{4, 15, 20, 23, 36, 37}	I7	Splice Site Deletion	I, II	2		
c.889+6T>G (c.992+6T>G, IVS7+6T>G, p.G279_294del) ^{26, 36, 37}	I7	Splice Site Deletion	Ib, III	2		
hSMN $\Delta 8^{23, 27}$	E8	Gross Deletion	II, III			
-455A>T ²		Transversion			Hinders transcription of SMN ²	
SV-D252A ⁵					Increased survival of SV-SMN-D252A-infected mice ⁵	<p>Abolished cleavage of SMN⁵</p> <p>Increased anti-apoptotic function of SMN in neurons⁵</p>

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