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A sequence compilation and comparison of exons that are alternatively spliced in neurons

Stefan Stamm*, Mike Q.Zhang, Thomas G.Marr and David M.Helfman
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA

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ABSTRACT

Alternative splicing is an important regulatory mechanism to create protein diversity. In order to elucidate possible regulatory elements common to neuron specific exons, we created and statistically analysed a database of exons that are alternatively spliced in neurons. The splice site comparison of alternatively and constitutively spliced exons reveals that some, but not all alternatively spliced exons have splice sites deviating from the consensus sequence, implying diverse patterns of regulation. The deviation from the consensus is most evident at the −3 position of the 3′ splice site and the +4 and −3 position of the 5′ splice site. The nucleotide composition of alternatively and constitutively spliced exons is different, with alternatively spliced exons being more AU rich. We performed overlapping k-tuple analysis to identify common motifs. We found that alternatively and constitutively spliced exons differ in the frequency of several trinucleotides that cannot be explained by the amino acid composition and may be important for splicing regulation.

INTRODUCTION

Among all animal tissues the brain is probably the most molecularly complex organ with about 30% of the mammalian genome expression dedicated to it [1]. Both kinetic [2] and clonal [3] analysis indicate that 40–65% of the mRNA expressed in brain is restricted to this tissue. Furthermore, the majority of this mRNA is expressed in neurons and not in glia [4], [5]. Neuron specific gene expression can be achieved by transcriptional (reviewed in [5, 6]) and post transcriptional mechanisms including splicing and RNA editing [7]. In order to analyze common features of neuron specific exons, we compiled and analyzed the currently available neuron specific exons.

It has been estimated that alternative splicing is involved in more than 5% of on/off regulation in Drosophila genes [8]. In addition, it has been shown that the inclusion of alternatively spliced exons alters the electrophysiological properties of ion channels like the the Glutamine A–D [9] and the NMDA [10] receptors. In 11 genes listed in this survey, alternatively spliced exons encode stop codons leading to truncated proteins. In 10 genes listed, the alternatively spliced exon introduces a phosphorylation site and in one case a phosphorylation site is removed.

The exact mechanisms that regulate the alternative use of neuron specific exons are not well understood. Several regulatory sequences have been identified, including splice sites deviating from the consensus [11], RNA binding factors [12, 13], elements in the flanking introns [14, 15] and secondary structures [16]. In addition, several components of the splicing machinery have been found to be specific for neurons, among them the composition of SR proteins [17], U2 RNA composition [18] and the protein SmN [19] that might be involved in the etiology of the Prader Willi syndrome [20], but whose functional significance is not clear [21].

Neuron specific alternatively spliced exons can be the result of neuron specific transcription followed by alternative splicing, or the result of transcription that takes place in all cells followed by neuron specific splicing. Although the consequence in both cases is an exon that is alternatively spliced in neurons, the mechanistic regulation might be quiet different. For example, neuron specific exons generated by neuron specific promoter use are alternatively regulated in non-neuronal cells [22]. In contrast, several genes exhibit neuron specific splicing only when expressed in neuronal cells, but not in any other cell type [11], [15, 23]. The neuron-specific usage of the exons compiled here has been established by comparison with some, but not all, non-neuronal tissues like liver or muscle. Therefore, more detailed investigations may detect some use of these exons in non-neuronal cell types. Furthermore, inspection of the compiled sequences shows that certain functional subclasses such as receptors are highly represented, which probably reflects the current focus of research on these molecules, rather than their greater use of alternative spliced exons.

METHODS

Collection of alternative spliced exons and control database

Exons that are alternatively spliced in neurons were collected from the literature using the Medline database, searching with the key words 'alternative splicing' and 'brain' or 'neuron'. The sequences were run against GenBank using the BLASTN 1.3.12

*To whom correspondence should be addressed

Table 1. Compilation of exons that are alternatively spliced in neurons

Mutually exclusive exons 

Gene	regulation	experimental evidence	accesion number	species	sequence	ref.
Glycine receptor α2A	regional and developmental	neuronspecific, in situ	X57281	R	ttgcattctgcag@GTCCTCCAGTAAACGTTACTTGCAATATTTTTATCAACAGTTTTGGATCAG TCACAGAAACCACCATGgtaagtgctacagt	[50]
Glycine receptor α2B	regional and developmental	neuronspecific, in situ	X61159	R	gttcaaattacag@GGCCTCCTGTAAATGTTACCTGCAACATATTTGGGTCAATAGCAGAAACTA CAATGgtgagtgggactgagcattga	[50]
Glutamate receptor, B type, flop	regional and developmental	neuronspecific, in situ, electrophysiology	M36419	R	atgttttatcgtttcaagA@AATGCGGTTAACCTCGCAGTACTAAAACTGAATGAACAAGGCCTG TTGGACAAATTGAAAAACAAATGGTGGTACGACAAAGGAGAGTGCGGCAGCGGGGGAGGTGATTC CAAGgtcagccccc	[9]
Glutamate receptor, B type, flip	regional and developmental	neuronspecific, in situ, electrophysiology	M38061	R	tattttccacgtgaagA@ACCCCAGTAAATCTTGCAGTATTGAAACTCAGTGAGCAAGGCGTCTT AACGACAAGCTGAAAAACAAATGGTGGTACGATAAAGGTGAATGTGGAGCCAAGGACTCGGGAAG TAAGgtcagttgctgcag	[51]
rat brain Ca channel, alpha subunit rbC-I		expression in brain, heart and adreanal gland	M67516	R	@GGTTACTTTAGTGATCCCTGGAATGTTTTTGACTTCCTCATCGTCATTGGGAGCATAATTGATG TCATTCTCAGTGAAACTAATgtgagtatc	[52]
rat brain Ca channel, alpha subunit rbC-I			M89924	R	ccccatgcag@CACTATTTCTGTGATGCATGGAATACATTTGACGCCTTGATTGTTGTGGGTAGC ATTGTTGATATAGCAATCACCGAGGTACAC	[52]
Ca channel α1, form 1		expression in brain and cardiac muscle, heart Northern analysis	L01776	M	@ATGCAAGACGCTATGGGCTATGAGTTGCCCTGGGTGTATTTTGTCAGTCTGGTCATCTTTGGAT CCTTTTTCGTTCTAAATCTGGTTCTCGGTGTTTTG	[53]
Ca channel α1, form 1		expression in brain and cardiac muscle, heart Northern analysis	L01776	M	@GTCAATGATGCCGTAGGAAGGGACTGGCCCTGGATCTATTTTGTAACACTAATCATCATAGGGT CATTTTTTGTACTTAACTTGGTTCTCGGTGTTTTGAGCGGGGAGTTTTCCAAAGAGAGGGAGAAA GCCAAAGCCCGAGGAGATTTCCAGAAGCTTCGAGAGAAGCAGCAACTAGAAGAAGATCTCAAAGG CTACCTGGACTGGATCACCCAGGCAGAAGACATTGACCCCGAGAATGAGGACGAGGGCATGGATG AAGACAAGCCTCGAAACA	[53]
Ca channel α1, form4		expression in brain and cardiac muscle, heart Northern analysis	L01776	M	@GGTTACTTTAGTGATCCCTGGAATGTTTTTGACTTCCTCATCGTCATTGGGAGCATAATTGATG TCATTCTCAGTGAGACTAAT	[53]
		expression in brain and cardiac muscle, Northern analysis	L01776	M	@CACTATTTCTGTGATGCATGGAATACATTTGACGCCTTGATTGTTGTGGGTAGCATTGTTGATA TAGCAATCACCGAGGTACAC	[53]
R15 cDNA	regional (ring ganglion)	neuron specific, in situ, protection	M17535	A	@TATATG	[54]
	regional (abdominal ganglion)	neuron specific, in situ, protection	M17536	A	@AGTGATGGAAGCGCAGAGAGAAGACCGTACACCAGGATGGGATCCGGG	[54]

casette exons, expression of the gene in all tissues, expression of the exons only in neurons 

Clathrin light chain B	developmental	expression in neurons, PCR, immunocytochemistry	L01564	R	tccttctctaacggttttcctcaagG@ATCGCTGACAAAGCGTTCTACCAGCAGCCAGATGCTGA TACCATTGGCTATGTgtacgtgcctcctttgctc	[11], [55]
Clathrin light chain B		expression in neurons immunocytochemistry	M20469	H	G@ATCGCTGACAAAGCATTCTACCAGCAGCCAGATGCTGATATCATCGGCTACGT	[56]
Clathrin light chain B			X04852	B	G@ATCGCTGACAAAGCATTCTACCAGCAGCCAGATGCTGATATCATCGGCTACGT	[56]
Clathrin light chain B			NA	M	gctgtctagG@ATCGCTGACAAAGCGTTCTACCAGCAGCCAGATGCTGATACCATTGGCTATGTg tatgttgca	[57]
Clathrin light chain A, LCA2		expression in neurons, Western blot, immunocytochemistry	M20471	R	G@GTGGCAGATGAAGCTTTCTACAAACAACCCTTCGCTGACGTGATTGGTTATGT	[55], [58]
Clathrin light chain A, LCA2			M20471	H	G@GTGGCAGATGAAGCTTTCTACAAACAACCCTTCGCTGACGTGATTGGTTATGT	[56]
Clathrin light chain A LCA2			X04849	B	G@GTGGCAGATGAAGCTTTCTACAAACAACCCTTCGCTGACGTGATTGGTTATGT	[59]
Clathrin light chain A, LCA1		neuronspecific, immunocytochemisrty	M15882	R	C@AAACATAAACCATCCTTGCTACAGCCTAGAACAGG	[55], [58]
Clathrin light chain A, LCA1			M20471	H	C@AAACATAAACCATCCTTGCTACAGCCTAGAACAGG	[56]
Clathrin light chain A, LCA1			X04849	B	C@AAACATAAACCATCCTTGCTACAGCCTAGAACAGG	[59]
neuronal cell adhesion molecule, exon 18	developmental	neuron specific immunocytochemistry	M15939	C	tctttcttcacagG@CACACCGCCGATACTGCAGCTACTGTTGAGGACATGCTGCCTTCTGTAACT ACGGGCACCACTAACTCTGACACTATCACTGAAACTTTTGCCACTGCTCAGAACAGCCCCACGAG CGAGACCACCACCCTGACCTCCAGTATTGCCCCGCCAGCCACGGCCATACCTGACTCAAACGCCA TGTCGCCTGGCCAGGCTACTCCAGCCAAAGCGGGAGCCTCCCCTGTCTCTCCACCACCACCCTCC TCTACGCCCAAAGTGGCCCCCCTTGTTGATCTCAGCGATACCCCAAGCTCTGCTCCAGCTACTAA TAATTTGTCTTCAAGTGTCCTGTCCAACCAAGGTGCAGTGCTGAGCCCCAGCACTGTTGCTAACA TGGCCGAGACCTCCAAAGCAGCAGCTGGTAACAAGTCAGCTGCCCCAACCCCTGCAAACCTCACT AGTCCTCCAGCTCCATCAGAGCCCAAGCAGGAGGTCTCAAGCACCAAGAGCCCCGAGAAAGAAGC TGCGCAGCCCAGTACAGTGAAGAGCCCAACAGAGACAGCCAAGAATCCAAGCAATCCGAAGAGTG AGGCTGCTTCAGGCGGCACCACAAACCCCTCCCAGAATGAGGACTTTAAAATGGACGAAGGGACC TTCAAGACACCAGACATTGATCTTGCAAAGGATGTTTTTGCAGCTCTTGGCACTACTACTCCTGC CAGTGTGGCTAGTGGGCAAGCTCGTGAGCTTGCTTCTTCCACTGCAGACAGCTCTGTACCTGCTG CACCTGCAAAGACCGAgtatggctgcct	[60]
neuronal cell adhesion molecule, VASE exon	developmental	neurons specific, also in heart and adreanal gland	M32611	R	ttgttctctccag@GCATCGTGGACTCGACCAGAGAAGCAAGAGgtatagcttacctgaccacta gcca	[61, 62],
neuronal cell adhesion molecule, VASE (π)exon			X14527	M	ttctctccag@GCATCGTGGACTCGACCAGAGAAGCAAGAGgtata	[63]
protein 4.1, exon 15		predominantly expressed in brain, PCR analysis	L00919	M	ttgaattgtggcaacgcag@AAGCTTGCAGGAAAAGGTGAAGATCTGATAAGAATGAGGAAGgtt agcctattttccctttc	[64]
Protein 4.1, exon 5		predominantly expressed in brain, PCR analysis	L00919	M	tgtcttcacag@AAACATGCTAATTTACAAGACTTGCTGAAGCGAGTGTGCGAGCACCTCAACCT TTTGGAAGAAGACTACTTTGGTTTAGCCCTGTGGGACAGCGCAACCTCTAAGgtaaggagac	[64]
nI src		neuron specific, Western analysis, PCR	M61224	C	tgctttcatgtagG@AGAAAAGTGGACGTCAGgtgtgtaccgag	[15], [65]
nI src		neuron specific, PCR	NA	F	G@AGGAAGATAAACTGCAG	[66]

(Table 1. *Cont.*)

nI src		neuron specific protection analysis	NA	H	ccttagG@AGGAAGGTGGATGTCAG	[67]
nI src		neuron specific PCR analysis	M61225	M	cgctgccccttagG@AGGAAGGTGGATGTCAGgtgtgtaccgagg	[15], [14]
sarc+ 1	developmental	neuron specific PCR analysis	M80900	X	ctgtgccatag@GAGACCTGACATAAGgtatgtgaccatcca	[68]
sarc+ 2	developmental	neuron specific PCR analysis	M80901	X	cacatgctgtgccatag@GAGACCTGACATGAGgtatgtgaccatacagcgaccatatttgtgcagctat	[68]
dopa decarboxylase	developmental	brain specific protection analysis	X04661	D	tttcaataatcgcacattctttcatattagctctaaccattcgagTTCATATCATTGCAAAAGTCAAACGAAAAGTAAATCTCTGAA@ATGAGCCACATACCCATTAGTAACACAATTCCAACAAAACAAACTGATGGTAATGGTAAAGCTAACATTTCGCCGGATAAGCTGGATCCCAAGGTTTCGgtatgtctattgggtttaggtatagagccaacaattatg	[69]
preprotackykinin, substance K		usage in brain, also in thyroid and intestine, protection analysis	X01399	B	gtatttttccagGG@CATAAAACAGATTCCTTTGTTGGACTAATGGGCAAAAGAGCTTTAAATTCTGgtatgtataaaa	[70]
preprotackykinin substance K		predominat usage in brain, protection analysis and primer extention	M34161	R	catatattcagaagcttgttaactttgtactagttatgagtttatttcttcaaaaacatacatactaaaatacccctaaatgtattttccagGG@CATAAAACAGATTCCTTTGTTGGACTAATGGGCAAAAGAGCTTTAAATTCTGgtatgtataaaatcatgtctgaaaatatgtaaatcaacttctgtaatttttacg	[16]
gephyrin, C4 form		brain specific, PCR	X66366 S38683	R	@GCTCGGCTTCCCTCGTGCTCATCTACCTATAGTGTATCTGAG	[71]
kinesin light chain, B form		brain specific, cDNA cloning	M75148	R	@GTGAGTATGAGCGTAGAGTGGAATGGG	[72]
exon destroys phosphorylation site						
Inositol 1,4,5, trisphosphate receptor	developmental	neuron specific PCR	M64699	R	@CAAATTTCCATTGATGAATTGGAAAATGCCGAGCTGCCACAGCCACCGGAAGCTGAGAACTCCACAGAGCAGGAGCTTGAACCAAGTCCACCCCTGAGGCAACTGGAAGACCATAAAAGG	[73]
exon introduces stop codon						
kinesin light chain, C FORM,		brain specific cDNA cloning	M75147	R	@ATGAGAAAGATGAAGCTCGGGCTGGTTAAATGACTTGCTCAGCGTCCATG	[72]
myelin associated glycoprotein (1B236), exon 12	developmental	neuron specific protection, in situ	M22357	R	ctgcatttccttcttcaatag@TCCAGAGAGGTCTCTACCCGGGATTGTCACTGAGAGCCCCAGGAGgtaggttccgggggccactgc	[74], [75], [76],
myelin associated glycoprotein, exon 12		brain specific, in situ	M74780	M	@TCCAGAGAGGTCTCTACCCGGGATTGTCACTGAGAGCCCCAGGAG	[77]
exon introduces phosphorylation site						
nII src	developmental	neuron specific protection	M34469	H	C@CAGACCTGGTTCACATTCAGATGGCTGCAAAGgtac	[78]
PROTEIN KINASE C βII	regional developmental	neuron specific in situ	M16829	R	ccccctctcatag@TGTGGGCGAAACGCTGAAAACTTCGACCGGTTTTTCACCCGCCATCCACCAGTCCTAACACCTCCTGACCAGGAAGTCATCAGGAATATTGACCAATCAGAATTCGAAGGATTTTCCTTTGTTAACTCTGAATTTTTAAAACCCGAAGTCAAGAGCTAAGTAGATCTGTAGACCTCCGTCCTTCATTTCTGTCATTCAAGCTCAACAGCTATCATGgtgacatttttttt	[79, 80]
PROTEIN KINASE C βI		brain specific, also expressed in tumor lymphocytes	M18254	H	cctctcatag@TGTGGGCGAAATGCTGAAAACTTCGACCGATTTTTCACCCGCCATCCACCAGTCCTAACACCTCCCGACCAGGAAGTCATCAGGAATATTGACCAATCAGAATTCGAATTCGAAGGATTTTCCTTTGTTAACTCTGAATTTTTAAAACCCGAAGTCAAGAGCTAAGTAGATGTGTAGATCTCCGTCCTTCATTTCTGTCATTCAAGCTCAACGGCTATTGTGGTGACATTTTTATGTTTTTCATTGCCAAGTTGCATCCATGTTTGATTTTCTGATG	[81]
exon introduces frameshift						
Oct 2.5		predominantly in brain, low levels in neurons	X57940	M	A@AGCACAATGGTGGGGTTGAGCTCTGGGCTGAGTCCAGCCCTCATGAGCAACAACCCTTTGGCCACTATCCAAG	[82, 83],
dopamine D3 receptor TM3del		neuron specific electrophysiology	M69190	R	ttttctctgccag@GTGACAGGTGGAGTCTGGAATTTCAGCCGCATTTGCTGTGACGTTTTTGTCACCCTGGATGTCATGATGTGTACAGCCAGCATCCTGAACCTCTGTGCCATCAGCATAGACAGgtgaggacaacaat	[84]

casette exons, expression of the gene in neuronal tissue where it is alternatively spliced 

NMDR receptor 1 exon 5	regional	neuron specific, protection analysis	S45121 L08228	R	attattcatcag@AGTAAAAAAAGGAACTATGAAAACCTCGACCAACTGTCCTATGACAACAAGCGCGGACCCAAGgtatatatgcat	[10], [85]
NMDAR receptor1, exon 21		neuron specific, protection analysis	X65227 L08228	R	GATAGAAAGAGTGGTAGAGCAGAGCCCGACCCTAAAAAGAAAGCCACATTTAGGGCTATCACCTCCACCCTGGCCTCCAGCTTCAAGAGACGTAGGTCCTCCAAAGACACG	[10]
dopamine D2 receptor (444)	regional	neuron specific, electrophsiology	M32241	R	cttcacag@GGCAACTGTACCCACCCTGAGGACATGAAACTCTGCACCGTTATCATGAAGTCTAATGGGAGTTTCCCAGTGAACAGGCGGAGAATGgtaagtgt	[86], [87], [88],
dopamine D2 receptor, D2A	regional	neuron specific, in situ	X51646	H	actccacag@GGCAACTGTACTCACCCCGAGGACATGAAACTCTGCACCGTTATCATGAAGTCTAATGGGAGTTTCCCAGTGAACAGGCGGAGAGTGgtaagtgctcaggcca	[89], [90]
dopamine D2 receptor, D2A		neuron specific, protection analysis	X55674	M	@GGCAACTGTACCCACCCTGAGGACATGAAACTCTGCACCGTTATCATGAAGTCTAATGGGAGTTTCCCAGTGAACAGGCGGAGAAGT	[91]
NaChannel I		predominantly brain, minor expressionin skeletal and cardiac muscle, protection	X03638	R	@GTGATAATAGATAAGCCAGCTACTGATGACAAT	[92]
NaChannel IIIb		brain expression protection analysis	S97388	R	GT@ATGTCATCCAGGATGGTGCCAGGGCTTCAGCAATGGGAAGATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTG	[92]
NaChannel IIIc		brain expression protection analysis	S97387	R	GT@TAGTCAG	[92]
tau , exon 2		neuron specific immunocytochemistry		H	tgtgttccagAA@TCTCCCCTGCAGACCCCCACTGAGGACGGATCTGAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGgtgggccccc	[93], [94]
tau, exon 3		neuron specific immunocytochemistry		H	tggttttagAT@GTGACAGCACCCTTAGTGGATGAGGGAGCTCCCGGCAAGCAGGCTGCCGCGCAGCCCCACACGGAGATCCCAGAAGGAACCACAGgtgagggtaa	[93], [94]
tau, exon 4		neuron specific immunocytochemistry	M93652	H	gactgggccgagaagggtccggcctttccgaagcccgccaccactgcgtatcctccacacagAG@CCTGAAAGTGGTAAGGTGGTCCAGGAAGGCTTCCTCCGAGAGCCAGGCCCCCCAGGTCTGAGCCACCAGCTCATGTCCGGCATGCCTGGGGCTCCCCTCCTGCCTGAGGGCCCCAGAGAGGCCACACGCCAACCTTCGGGGACAGGACCTGAGGACACAGAGGGCGGCCGCCACGCCCCTGAGCTGCTCAAGCACCAGCTTCTAGGAGACCTGCACCAGGAGGGCCGCCGCTGAAGGGGCAGGGGGCAAAGAGAGGCCGGGGAGCAAGGAGGAGGTGGATGAAGACCGCGACGTCGATGAGTCCTCCCCCCAAGACTCCCCTCCCTCCAAGGCCTCCCAGCCCAAGATGGGCGGCCTCCCCAGACAGCCGCCAGAGAAGCCACCAGCATCCCAGGCTTCCCAGCGGAGGGTGCCATCCCCCTCCCTGTGGATTTCCTCTCTCCAAAGTTTCCACAGAGATCCCAGCCTCAGAGCCCGACGGGCCCAGTGTAGGGCGGGCCAAAGGGCAGGATGCCCCCCTGGAGTTCACGTTTCACGTGGAAATCACACCCAACGTGCAGAAGGAGCAGGCGCACTCGGAGGAGCATTTGGGAAGGGCTGCATTTCCAGGGGCCCCTGGAGAGGGGCCAGAGGCCCGGGGCCCCTCTTTGGGAGAGGACACAAAAGAGGCTGACCTTCCAGAGCCCTCTGAAAAGCAGCCTGCTGCTGCTCCGCGGGGGAAGCCCGTCAGCCGGGTCCCTCAACTCAAAGgtctgtgtcttgagctttcttcgctccttccctggggacctcccaggcctcccaggctgcgggcactgccactgagcttccaggcctcccgactcctgctgcttctgacgttcctaggacgccactaaatcgacacctggg	[93]
tau, exon 6		neuron specific immunocytochemistry	X61371	H	tatgtttatgtttaag@ACATCCACACGTTCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTTAGCCCCAAACTCCCCACTCCTGGTAGCTCAGACCCTCTGATCCAACCCTCCAGCCCTGCTGTGTGCCCAGAGCCACCTTCCTCTCCTAAACACGTCTCTTCTGTCACTTCCCGAACTGGCAGTTCTGGAGCAAAGAGATGAAACTCAAGgtaaggaaactct	[93]

(Table 1. *Cont.*)

tau, exon 8		neuron specific immunocytochemistry	X61375	H	tttttctctttaagCG@ACTAAGCAAGTCCAGAGAAGACCACCCCCTGCAGGGCCCAGATCTGAG AGAGgtactcgggagcc	[93]
tau, exon 10		neuron specific immunocytochemistry		H	tctggctaccaaag@GTGCAGATAATTATTAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTG TGGCTCAAAGGATAATATCAAACACGTCCCGGGAGGCGGCAGTgtgagtaccttcac	[95]
big tau	regional, peripheral nervous system	neuron specific, in situ hybridization, Northern analysis	M84156	R	AA@CCGCAGAAGGTCGAGATTTTCTCACAAAGTTTGCTTGTCGAACCAGGGCGTCGTGAAGGCCAGGCCCCAGATT CAGGGATCTCAGACTGGACCCACCAACAGGTGCCTAGCATGTCTGGGGCTCCCCTCCCGCCACAAGGCCTCAGAGA GGCTACACACCAACCTTTGGGAACAAGACCTGAGGATGTAGAGAGAAGTCACCCGGCCTCTGAGCTGCTGTGGCAA GAGTCACCTCAGAAGGAAGCCTGGGGCAAAGACAGGCTGGGAAGTGAGGAGGAGGTGGACGAAGACATCACCATGG ACGAATCGTCCCAGGAATCCCCTCCCTCCCAAGCCTCCCTGGCCCCTGGCACGGCCACCCCTCAGGCCCGCTCCGT TTCTGCTTCCGGGGTCTCTGGGGAGACCACTAGCATCCCTGGATTCCCAGCTGAGGGTTCCATCCCACTTCCTGCT GATTTCTTCTCCAAAGTCTCCGCAGAGACCCAGGCCTCACCGCCAGAAGGGCCTGGCACGGGGCCCTCGGAGGAAG GGCACGAGGCTGCCCCTGAGTTCACATTCCACGTGGAAATCAAAGCCAGCGCGCCGAAGGAACAGGATTTGGAAGG GGCTACAGTGGTGGGGGCCCCTGCAGAGGAGCAAAAGGCCCGAGGCCCCCTCTGTGGGAAAGGGCACGAAAGAGGCT AGCCTTCTGGAACCAACTGACAAGCAACCTGCAGCCGGCCTGCCAGGAAGGCCAGTCAGTCGGGTTCCTCAACTTA AAA	[96]
tau		neuron specific,	M26157	B	attttttcttttaagCA@ACCATGCAAGTGCAGAAAAAACCACCCCCTGCAGGGGCAAAATCTGA GAGAGgtaatt	[97]
microtuble associated protein map 2C	developmental	neuron specific immunocytochemistry	X17682	R	@GCACTGGAAGAAGCAACAAGTGGTGAATCAGC	[98]
Neurexin III alpha		brain specific, Northern analysis	L14851	R	@GGTAGAAGTAAA	[99]
Neurexin III alpha		brain specific, Northern analysis	L14851	R	AC@TGTATCAGGATAAACTGTAACTCCA	[99]
Neurexin III alpha		brain specific, Northern analysis	L14851	R	@GGCAACACTGATAATGAACGCCGCCAAATGGTAAAACAGAAAATCCCCTTCAAATATAATCGGC CTGTAGAGGAGTGGCTGCAGGAAAAA	[99]
Neurexin III alpha		brain specific, Northern analysis	L14851	R	GT@AGGTCAG	[99]
Ca- Calmodulins Dependent Kinase, ß subunit	regional	brain specific, Northern analysis	M16112	R	@GAGCCTCAAACCACCGTTATCCATAACCCAGTGGACGGCATTAAG	[100, 101]
glial growth factor, exon 5		neuron specific in situ	L12261	H	@GAGATCATCACTGGTATGCCAGCCTCAACTGAAGGAGCATATGTGTCTTCAGAGTCTCCCATTA GAATATCAGTATCCACAGAAGGAGCAAATACTTCTTCA	[102]
glial growth factor, exon 5		neuron specific	L12259	B	@GAGATCACCACTGGCATGCCAGCCTCAACTGAGACAGCGTATGTGTCTTCAGAGTCTCCCATTA GAATATCAGTATCAACAGAAGGAACAAATACTTCTTCAT	[102]
intergrase like protein FE65		neuron specific protection and northern analysis	X60468	R	cggacccagA@GAGAGgtattaacgtcca	[103]
exons containing stop codons						
NMDA receptor 1		neuron specific electrophysiology	S39221	R	CCCTCTGTCCATCACACAGGTCGGAAAGAGCAGGCCCGCAGCACCAAATGTAATACAAGTTGCCT GCAGCCAGTTGCAGAGGCGGTGAACATTCTATCCCTACAATGCACTGCCCCTGACCACCAAGAGG GAACCGGTAAAAAACTAACCTAGAAGCATCAGAGGGCCAAGAGCAGTGTGAATCATGACGGTGCG GAAGGAGCCATGTTCACTCA	[10]
NEUREXIN III ALPHA		brain specific Northern analysis	L14851	R	CC@AGAAGCTCTAATGCAGCTAGGATCACTCCGTGCCGCCCTTACATGGACATGGCGACTCACTT ACACATTTACCCTTCTCATCTTCATCTCCTGTGTAGTACACTCATAGACACACCCCTCCCCTTTC CGCACCCCTTCTTTCCCATGCTCCCCCCTTCTTTAGCGTTGTTAAAATTTATGTGCTGTCATCCA CCCCCCTAAATTAAGAAAAATCTCAAAATTTGTCAAAAAGACAATACAAATCTAAATATTTATCT GAAAACTAACAATGAAGAAATTCATTCCAAATCCTATAGATGCATAGATTTTTTTTAAGGCAAAT TATAATTTTTTCACTTTCAG	[99]
NEUREXIN III ALPHA		brain specific Northern analysis	L14851	R	TC@CTAGAAAGAAGAATTATTTTAAATTTAAAAACCAATGCCCATCCTAAGTCCCTCCAAAGTAA AACTTGTTAAAGTGCAGATTTTTTTCTTTTCATGTTATGTGGTGTGAATGTTTGTGTTGTTGCCT CCCTGTATCATCCTCTGTTGTAAATTACTATATCTGAAAAACTAG	[99]
NEUREXIN III ALPHA		brain specific Northern analysis	L14851	R	@ACATTTTGCTCAAAAGTTTTTAAGAAATAACAACAATAACAACAACAACAG	[99]
NEUREXIN III ALPHA		brain specific Northern analysis	L14851	R	CA@ACTACAACAACAAAAAAAAGCAACTTTCAAGAATGTGGCAATTCTATTTGTCCAAGAGCATT CTTACACAACTTTCTTTTGTAAATTTTTTCTTCCATGCCAAAAAACATGCGGGCAATTTGTTGAT GAGGTGAATTAGTTATTCCTCTTCTTGTAGAAGACCCTTTAGCTACCCCTCCTATTGCTACTCGT GTACCCTCCATTACACTCCCCCCTACCTTCCGCCCCCTCCTCACCATTATTGAGACCACCAAAGA TTCCCTGTCCATGACCTCTGAGGCGGGGTTACCTTGCCTGTCGGACCAAGGCAGCGATGGTTGTG ATGATGATGGCTTGGTGATATCTGGGTATGGCTCAGGGGAAACCTTTGACTCTAACCTGCCCCCT ACTGATGATGAAGATTTTACACCACCTTCTCCTTGGTAACAG	[99]
NEUREXIN III ALPHA		brain specific Northern analysis	L14851	R	AT@AAGAGTCTTTCCACTTCAATCTTCGAAGGTGGCTACAAAGCGCATGCGCCCAAGTGGGAATC CAAGGACTTTAGACCTAACAAAGTCTCGGAAACTAGTAGAACTACAACCACCTCTTTGTCCCCTG AGCTGATCCGCTTCACAGCGTCCTCCTCGTCTGGGATGGTGCCCAAATTGCCAGCTGGCAAAATG AATAACCGTGATCTCAAACCCCAGCCTGATATAGTCTTGCTTCCGTTGCCCACTGCCTATGAGCT AGACAGCACCAAACTGAAGAGCCCACTAATTACTTGCCCCATGTTCCGTAATGTGCCCACAG	[99]
glutamic acid decarboxylase	developmental	neuron specific in situ	M38351	R	cttcctttatcagG@CCATCAGACATGAGGGAGTGTTGGTTGCTACGGTGATGGGGCTCAGAGCA GGACCAAAGCATGAGTGTGGCCTCCAGAGGTGATGgtaactgaacactgtt	[99]
exon introduces a frameshift						
Choline Acetyltransferase		neuron specific immunocytochemistry	S45018	H	@TTCTTTGTCTTGGATGTTGTCATTAATTTCCGCCGTCTCAGTGAGGGGGATCTGTTCACTCAGT TGAGAAAGATAGTCAAAATGGCTTCCAACGAGGACGAGCGTTTGCCTCCAATTGGCCTGCTGACG TCTGACGGGAGGAGCGAGTGGGCCGAGGCCAGGACGGTCCTCGTGAAAG	[104]
exons containing a phosphorylation site						
GABA A receptor, γ 2 subunit	regional developmental	neuron specific electrophysiology	X15376	H	cccaaag@CTTCTTCGGATGTTTTCCTTCAAGgtataat	[105]
GABA A receptor, γ 2 subunit	regional developmental	neuron specific	X54994	C	@CTTCTTCGGATGTTTTCCTTCAAG	[106]
GABA A receptor, γ 2 subunit		neuron specific	M55563	B	@CTTCTTCGGATGTTTTCCTTCAAG	[105]
GABA A receptor, γ 2 subunit	regional developmental	neuron specific	M62374	M	tccaaag@CTTCTTCGGATGTTTTCCTTCAAGgtatactgttttt	[107, 108]
L1 neuronal cell adhesion molecule	regional	neuron specific PCR, northern analysis	X59149	R	@GTCCAGTTCAAT	[109]

alternative 3' splice site  , **all genes are only expressed in neuronal tissue, the alternativly spliced exon is underlined**

GlyReceptor α1	regional developmental	neuron specific immunocytochemistry		R	cttattttaagtag@AGCCCCATGCTAAATCTGTTTCAGGATGATGAGGGTGG	[110]
NMDA Receptor 1, exon 1		neuron specific, electrophysiology	X63255	R	CTGAGACGCCCCGCCCGCCCTCCTCTGCCCCTCCCCCGCAGACAGACGCACGGGACAGCGGCCTG GCCCACGCAGAGCCCCGGAGCACGACGGGGTCGGGGGAGGAGC	[10]
D3 receptor, D3S	regional	neuron specific pharmacological profile	X67274	M	tcttccctttcag@GAGCACATAGAAGACAAACCATATCCCCAGAAATGCCAGGACCCTCTCTTG TCACATCTACAGCCCCTCTCTCCTGGCCAGACACAT	[111]

(**Table 1.** *Cont.*)

D3 receptor(o2del)		neuron specific, electrophsiology	M69192	R	accacagGG@GATCCCAGCATCTGCTCCATCTCCAACCCTGATTTTGTCATTTACTCTTCAGTGG TGTCCTTCTACGTTCCCTTCGGGGTGACTGTCCTGGTC	[84]
POMPC		neuron specific	J00291	H	cattgttttgtccttgcagGGGTCCCACGAATCTTGTTTGCTTCTGCAG	[112]
prolactin	regional	expressed in pituritary neurons immunocytochemistry	J00767	R	cactgatacctgaatttctttagCAG	[113]
nervous system specific RNP protein-1	developmental	neuron specific, in situ	M34894	X	attactttataaacaagGC@TCCACTCCAACCCGCACAGGGGGGTTTCTTGGAAC	[114]
exon introduces frameshift						
Synapsin I	regional	neuron specific, immunocytochemistry	M27812	R	ccttgtctctctctagC@AAATCCCAGTCTCTGACCAATGCCTTCAACCTTCCAGAGCCAGCCCC	[115]
Synapsin I	regional		J05431	H	tccaccttgtctctctctagC@AAATCCCAGTCTCTGACCAATGCCTTCAACCTTCCAGAGCCAG CC	[116]

alternative 5'ends

γ-aminobutyric acid A receptor ß4' subunit		neuron specific	X56647	C	G@TGAGAGAGCAGgtttgtccccttc	[117]
raw2 (NGK2, Kv3.1 b)		neuron specific, electrophysiology	Y07521	M	GT@AGGAAACCTCTCAGAGGCATGTCGATCTGACCTTTCACCTCCGCCCCCTGTAGCAATGATTC CAGATCCAGTCAGACTGCTT	[118],
exon introduces a stop codon						
GLIAL GROWTH FACTOR		neuron specific	L12259	B	GT@AAGAGATGCCTACTGCGTGCTATTTCTCAGTCTCTAAGAGGAGTGATCAAGGTATGTGGTCA CACTTGAATCACG	[102]
exons introducing a phosphorylation site						
H tyrosine hydroxylase, HTH-2		neuron specific immunocytochemistry	M18115	H	@GTAAGAGGGCAGgtaggtgccc	[119], [120], [121, 122]

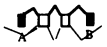
alternative 3' and polyadenylation

α tropomyosin, exon 9c	regional developmental	neuron specific immunocytochemistry	M34138	R	cctcttccttctgcctcttcttttctgctaacccttgctgacctgcccagAT@CAACTCTACCAT CAACTCGAGCAAAACCGCCGTCTAACTAATGAACTAAAGCTGGCCCTGAATGAGGATTAAAACCC TGGGCCAAG	[23], [123]
α tropomyosin, exon 9c, BRT-1		brain specific, protection	M64288	C	tctttctcttcccaccggcgctgatgtctctgtttgctctagAG@CGCTCCCGGCAGGAGGCCGA GAAAAACCGCGTTCTCACTAACGAGCTGCGAGTCATCCTTACCGAGCTTAACAACTGAGCT	[124],
neuroglian	regional developmental	neuron specific immunocytochemistry	M28231	D	A@CAATTTACCGAGGATGGCTCCTTCATTGGCCAATATGTTCCTGGAAAGCTCCAACCGCCGGTT AGCCCACAGCCACTGAACAATTCCGCTGCGGCGCATCAGGCGGCGCCAACTGCCGGAGGATCGGG AGCAGCCGGATCGGCAGCAGCAGCCGGAGCATCGGGTGGAGCATCCGCCGGAGGAGCAGCTGCCA GCAATGGAGGAGCTGCAGCCGGAGCCGTGGCCACCTACGTCTAAGAGGCGTGGCTGGGATTCACT TGCCCCATTGTTCTCCCTGATTTTCTACCAAACGATTCAAACGCCTCTTAAACAAAAAAGAAACT GTGTAATTCTATGTGTAAAACGAAAACTGCTTTAAGTGTCT	[125]
Calcitonine gene related peptide, CALC-I gene		neuron specific neuro peptide expression	N00016	R	catcctgaatatcagT@GTCACTGCCCAGAAGAGATCCTGCAACACTGCCACCTGCGTGACCCAT CGGCTGGCAGGCTTGCTGAGCAGGTCGGGAGGTGTGGTGAAGGACAACTTTGTGCCCCACCAATG TGGGCTCTGAAGCCTTCGGCCGCCGCCGCAGGGACCTTCAGGCTTGAACAGATAATAGCCCCAGA AAGAAGgtgacttccttgtacaactgg	[126], [127], [128], [12]
B23.2		brain specific cDNA cloning	M37039	R	ctatctccttggtttaattgcag@GCGCATTGAACATTCCTGGGCACTACTGGTAAATTAAGCCC AAAGATGGGGAAAGAGGAAAAGGAGAAACAAATATAGTACCATCAACAATCCAGACTGAAGTCTT CTATTTTAATCTCAATCCCCTTTCCTGATTGGCCATCCATTCCCCCTTGCAGGCTGGAAGCAATC GTTTTCCTAAAGCATTTTTCTTTTTCACTCGTGTGATGCAGAAAACTTGACTGCTTTTCTATACC ACTTGTGCATATGCCTTAACTCTGACCATGTTTTAATTTTAACCTTTGTATCCTTAGCTGCTCGA AATAAATTTTTGAATGAACCAATAAGGATgtatgtgacaatatttttaaattgtagtgaattatc ttctaggtgatggaggcaatttaagtactca	[129]
raw2 Kv4 isoform		neuron specific in situ, electrophysiology	M68880	R	AT@TCCAAACTGAATGGGGAGGTGGCGAAGGCCGCGCTGGCGAACGAAGACTGCCCCCACATAGA CCAGGCCCTCACTCCCGATGAGGGCCTGCCCTTTACCCGCTCGGGCACCCGCGAGAGATACGGAC CCTGCTTCCTCTTATCAACCGGGGAGTACGCGTGCCCGCCTGGTGGAGGAATGAGAAAGG	[130]

pairwise mutually exclusive

GO alpha, exon 7B		mainly in brain, less in heart and lung, Northern blot	M60161	H	cccctccactctgttgcag@AACCGCATGCACGAATCCCTGAAGCTTTTGACAGCATCTGCAAC AACAAATGGTTCACAGACACGTCCATCATCCTGTTTCTTAACAAGAAGGACATATTTGAAGAGAA GATCAAGAAGTCCCCGCTCACCATCTGCTTTCCTGAATATACAGgtagagacccc	[131],
GO alpha, exon 8B		mainly in brain, less in heart and lung, Northern blot	M60162	H	tgccttgttttgctctgcagGC@CCCAGCGCCTTCACAGAAGCCGTGGCTTACATCCAGGCCCAG TACGAGAGCAAGAACAAGTCAGCCCACAAAGAGATCTACAGCCACGTCACCTGCGCCACGGACAC CAACAACATCCAGTTTGTCTTTGATGCTGTGACGGACGTCATCATCGCCAAAAACCTGCGGGGCT GTGGACTCTACTGAGCCCAGCCGCCCTGCCCGGCACCCTTGCCCTGCCTGGCCTGCCGCCCCCCC CTCCCCCTGGAACCAAGCTCCACCAGTCTCAG	[131],
GO alpha, exon 7A		mainly in brain, less in heart and lung, Northern blot	M60163	H	tcccttcctgcggccgcag@AACCGCATGCACGAGTCTCTCATGCTCTTCGACTCCATCTGTAAC AACAAGTTCTTCATCGATACCTCCATCATTCTCTTCCTCAACAAGAAAGATCTCTTTGGCGAGAA GATCAAGAAGTCACCTTTGACCATCTGCTTTCCTGAATACACAGgtgggtgcca	[131],
GO alpha, exon 8A		mainly in brain, less in heart and lung, Northern blot	M60164	H	tcttctgtgtcttgttacagGC@CCCAATACCTATGAAGACGCAGCCGCCTACATCCAAGCACAA TTTGAAAGCAAAAACCGCTCACCCAACAAAGAAATATATTGTCACATGACTTGTGCCACAGACAC GAATAACATCCAGGTGGTGTTCGACGCCGTCACCGACATCATCATTGCCAACAACCTCCGGGGCT GCGGCTTGTACTGACCTCTTGTCCTGTATAGCAACCTATTTTGgtaatgattccagcacccacag aacagcttgcgtgcgcgcgcatacacacac	[131],

(**Table 1.** *Cont.*)



Distant coordinated expression

Agrin, exon A		only in neurons exon A and exon B simultanously used PCR analysis	M97371	C	@AAATCCCGTAAG	[132]
Agrin, exon B		only in neurons exon A and exon B simultanously used PCR analysis	M94271	C	T@CCCGACGCATTGGACTACCCTGCTTGAGCCCAG	[132]

retained intron

FMRF-2,	regional	neuron specific, immunocytochemistry	M14958	A	G@TTCGGGAAAAGGTTTATGCGATTTGGAAGGGGCTCCAGCGATGATGATGAAAGTGGTGATGAC GATGTGCAGGATCTGACGGATATTGGTGATGGTCTTGGGGGCGAAGGGGAAGTAAATAAACGGTT CATGAG	[133]

gene structure unknown

Calcium channel α 1, Form2		expressed in brain and cardiac muscle Northern analysis	L01776	M	@AGAGGCGCTCCAGCGGGCTTGCATGATCAGAAGAAAGGGAACTTTGCTTGGTTAGTCACTCTAC AGAAACCCATGTG	[53]
Calcium channel α 1, Form3		expressed in brain and cardiac muscle Northern analysis	L01776	M	A@CCGGCCAG	[53]
α 1 Calcium Channel		expressed in brain, heart and lung, Northern blot	M57682	R	@GTGAAGGCGAGACCCAGGGATGCTGTGGAAGTCTCT	[134]
DHP sensitive Ca-Channel, rB-α 2		brainspecific cDNA cloning	M86621	R	@AAAATGAAGGATTCAGAAACC	[135]
rawI R shaw homologue		neuron specific, in situ	M34052	R	AT@AACTGCAAAGATGTTGTCATTACTGGTTACACGCAAGCCGAGGCCAGATCTCTTACTTAATG ACTTGGGAAAGGCACAAAACATGAAAGAAAG	[136] ,[137],
raw I, Kv3.2b		neuron specific, in situ,	M59211	R	GA@TATGAAAAATCCCGAAGCTTAAACAACATAGCGGGCTTGGCAGGCAATGCTCTGAGACTCTC TCCAGTAACATCCCCCTACAACTCTCCGTGTCCCTCTGAGGCGCTCTCGGTCTCCCATCCCATCTA TCTTGTAAACCAAACTGCACCAATCGGCTAAATTCTATCACTACAACTCCTGTCCACCCTGTACT GGAAACAATTAACTATAGAGTTTCTCCAGGCTCCATTAAGAACAGTGTAGATCCTGCATGACATT ACTATTCGAAGTCAGAAATGCTACTCGAGTAGCTAGAACATCTTTTCCTGGCTTTAAAGATGGCC TAAAGTAGTGCTGCTACTCAGTAAGAGTTGCCCAATTTCCTTTCGCTATACGGTGACCAATAGCG TCAGATATTGGCCAGTGCACGAATGCATAAGCAAATCTTCAGGGAGATATTCTTTAATAGTGTGC TTCTAAATGCCAACCACTTCACTGGACCTTCCTTTCTTGTGACTGACTCCAACCCATTCTGAAGA TGTCTACGGGATCCTATCTAGATCGTATAAACCATGACTTTGGTCAGCTCGTTTGCATGGACCAT CTTGCCTGTATCACCTGAATACAGTGTGTAGCGTCCTGGTACC	[138],
raw I, Kv3.2.c,		neuron specific, in situ	M59313	R	CA@AGCACACTAGAGCCCATGGAGAGTACTTCACAGACTAAAGGAGACACGAGACCAGAAGCTCA CTGGAATTGTGCGCATTTACTCAATTTTGGCTGTCCTACGGGAAGTTCATTTCCCACCCTCTAAG TGTTCGGTGGAACTGCCAAACGTTTATTTCCAAAGCTGTGTGGTGATAGGACTCCATTTTCATTC CCGTGTCTTGCTCTCCACGTTACGTCACGCTTTGTATGAGACGCGCCCCCAGCTCATCCAGCTGC CTCTAATAGTCTACTGAAAATGCGTATGACTGCCTTCAAAGGTCACAGGATGGGGTCCTGGTTGG AGTGGTTAGGGAAATCCACCAAGCTCGTGTTCCTGAGAAGCTGTTTGATTATCTAAGTACACGGC TACCACCAACAATAGATTAGGTTGAGAATTATTGGTTAAAATAAAATTGACCTTAGTTCGTGGAG GGAGAGGGAAAGAGAGGAAGTCATCTGCATACATCAAATTCAGATCTATTTCGCTAAAATTATGA CTCGGTTTACATTCCATTGCGTTCCTTTTTATTTAATTTAATTTTATTACCTAAGGGATTGGTAA TGTGCTTTCCATCCTGAATCACGTGGATAATGGCACCCAATGCCATTATTCTATGAATCACTCTT TTAAACTAACTAGTAAACCTTAAAAATACATGTTGGAAACAAGTGCACACCTGTAGGTTAAGCAT GCTTCATTAATTAATCATACCTAAAATTTAAAAGAATGTATCTCCTATATTTTTAATTTTTTAGA AACATGTCCTGAAAATTTAAAAGTGTTTAGTCTGTAAACTTACTTAAGGCCTTTTTTTTTTTTTG GCCTAATTTTCAAAAGTTCTTGTAGTCTCTATGCCAAAATCATGTCAGTACTAATTATGATCGAG CATAAATATGTTTTGAAAGACTGTAGCTATAATTTGTTATAGCTGGTTTAATTTTTTTCAGAATG TGTGAATTGTGTCAATATTGAATTC	[138],
α-4 Acetylcholine Receptor , 4.1 isoform		neuron specific in situ	M15681	R	CT@TGCTGATGGCTTCGACAGTGTTCTCAGGCTCACGTCTCCTGCTGACTTTGTTTCCCAG	[139]
α-4 Acetylcholine Receptor , 4.2 isoform		neuron specific in situ	M15682	R	GT@ATGATCTAGGGACGTGGTGGTGCCCAGCTCCCACATCTCTGTAGGGCCATACGACTCGTCAG TCACCCACATCTTCCAAACCGGCTGACCATGAGACACCCTAGGAGAGAGATGATGCTTCTTGGGA GATG	[139]
myelin associated glycopotein MAG, exon 2	developmental	brain specific Northern analysis	M74780	M	CCTTCTGTGTTAGCGTTCCTCAGCTCCTCATTGCAGTTCCCTGAAGAGACTTG	[77]
Neurexin II ALPHA		neuron specific in situ, protection	M96376	R	ACGCAGGGATTGGACACGCTATGGTAAACAAACTGCATTATCTG	[140]
Neurexin II ALPHA		neuron specific in situ, protection	M96376	R	GTGCTGCAG	[140]
Neurexin II ALPHA		neuron specific in situ, protection	M96376	R	GGAACTTTGATAACGAGCGCCTGGCGATTGCTAGACAGAGAATCCCCTACCGGCTTGGTCGAGTA GTAGATGAATGGCTGCTCGACAAAG	[140]
Neurexin II ALPHA		neuron specific in situ, protection	M96376	R	CGACGAGGGCTCCTACCAAGTGGACCAGAGCCGGAATTACATCAGTAACTCGGCCCAGAGCAATG GGGCGGTGGTGAAGGAGAAGGCCCCCGCTGCCCCCAAGACGCCCAGCAAGGCCAAGAAGAACAAA GACAAAGAGTATTACGTCTGAGCACCCAGTCCAGGCACCGCGCCCCACTGCCAGCTGCTCCTCCC GGGAAGGCCCGGGAGGAGGGTGCGGCCCTCTCCCTGCAGGGGGATCTGGGGACCCTCTCCCCGGC TGCCTCAGGCTTCTCCCACGAAGAGGAAACGCAAAAAGAAAAGGAATATAACTACTACGTGCTCA TCCCCTTCCCTCCCACTGCCCTCGGCGCCGCACTGTCAGCTCTGGGGCTGGCTGTCCTCCGCTCT GCGCCTGTCAGGCAGGGCACGTGCTCACAGCCCTGGGTTGATTTATTTTTTAAGGGGCGTAGTTT TATTTTGGTGGGGCTGGGCGGGAAGGAAGGCTGGGGTTTTGTAAAGTGTCCACTGCGCCGTTCGT TTATTTCCCTCGATTTTCTTCTTCCTCCCAGCTCCTCCCGCCTTCCTTCTTCGCAGCCCTCCTGT CCTGGTTCAGGCTTGCTGTGTCTTTTGTCCCTACCCTCCTCCACCCCATCCCCCCTTTCTTTCCT TTTCTTTTCTCTTCTTTTCCTTTCTTTCTTTTTTAAATTCTGTTTTCTCTGCTTCCCTTCCTTTG GGTTTCCAGAGTCGCTGGGAGAAGAAGGGTGGGCTTGGGTGGCTGGGGCCGGGCAGTGGGGCTCA TTCCCCTG	[140]
Neurexin II beta		neuron specific, in situ, protection	M96377	R	GAGGAGAGTTAATATTGCCCATTATCACGGAGGACTCCTTAGACCCCCCTCCCGTGGCCACCCGG TCCCCCTTCGTGCCCCCGCCCCCCACCTTCTACCCCTTTCTCACGGGCGTGGGTGCCACCCAAGA CACCCTGCCTCCGCCCGCCGCGCGCCGCCCGTCCTCCGGGGGCCCGTGTCAGGCCGAGCGCGACG ACAGCGACTGCGAGGAGCCCGTGGAAGCCTCGGGCTTCGCCTCCGGGGAGGTCTTTGACTCCAGC CTCCCCCCCACGGACGACGAGGACTTTTACACCACCTTCCCCTTGGTCACGGACCGCACCACCCT CCTGTCACCCCGCAAGCCTGCGCCCCGACCTAACCTCAGGACAGATGGGGCCACGGGCGCCCCCG GGGTGCTACTTGCGCCCTCCGCCCCAGCCCCCAACCTGCCCGCGGGCAAAATGAACCACCGAGAC CCACTGCAGCCGCTGCTGGAGAACCCACCCCTGGGGCCTGGGGTCCCCACGGCCTTCGAGCCGCG GCGGCCGCCTCCCCTGCGCCCCGGCGTGACCTCAGTCCCCGGTTTCCCCCGTCTGCCCACAG	[140]
NeurexinI alpha		neuron specific, in situ, protection	M96374	R	GACAACAATGTAGAAGGTCTGGCGCACCTGATGATGGGCGACCAAGGTAAAAGTA	[140]

(Table 1. *Cont.*)

NeurexinI alpha		neuron specific, in situ, protection	M96374	R	CACTCAGGCATTGGACACGCTATG	[140]
NeurexinI alpha		neuron specific, in situ, protection	M96374	R	ATTGTATCAGGATTAACTGTAATTCCA	[140]
NeurexinI alpha		neuron specific, in situ, protection	M96374	R	GAAACAATGATAACGAGCGCCTGGCGATTGCTAGACAGCGAATTCCATATCGACTTGGTCGAGTA GTTGATGAATGGCTACTCGACAAAG	[140]
NeurexinI alpha		neuron specific, in situ, protection	M96374	R	GTGGGTTAG	[140]
Drebrin	developmental	neuron specific immunocytochemistry	M36961	C	@GGCAGCCAGTCCGACTACCGAAAGGTTTCGGCAGCGGGCTGCAGCCCCTGCGAGTCCAGCCCGG CCTCCACGCCGCTGGGCGAGCAGCGCACCCGCGCCCCGGCCGAAGAGACGCCGGCAACGCCCAAA	[141]
Calcieurin A, PP2B α2		brain specifc cDNA cloning	M29550	H	@CATGTTCTAGGCACTGAAGACATATCGATTAATCCTCACAATAATATTAATGAG	[142]
Calcineurin, PP2B α1	regional	brain specifc, also expressed in thymus	J05480	M	@GCTACTGTTGAGGCTATCGAGGCTGATGAA	[143]

Regional distribution indicates the alternative splicing is different in the various regions of the brain. Developmental regulation indicates a regulation during embryonic and early postnatal development. Experimental evidence lists the experimental methods employed to determine the specificity (in situ: RNA *in situ* hybridisation). If the alternative spliced exons were found to a lesser extent in other tissues, it is indicated under 'experimental evidence'. A '@' sign in the sequences indicates the beginning of a codon. The species are abbreviated as follows: R: rat, M: mouse, H: human, D: drosophila, B: bovine, C: chicken, F: fish. The accession number refers to GenBank. Exon sequences are indicated by capital letters, intron sequences by small letters.

program (NCBI) [24] to find related sequences and entry errors. Vertebrate internal exons and their corresponding downstream donor sites were obtained from the GeneId-datasets [25]. The vertebrate acceptor sites were kindly provided by Dr Knudsen (CEDB, West Florida). In order to produce scores for the combined 5′ and 3′ splice sites, we randomly selected 200 Genbank (80.0, 12/10/93) vertebrate splice site pairs that flank constitutively spliced exons. cDNA sequences upstream and downstream of the alternatively spliced exons were extracted from Genbank as control sequences for constitutively spliced exons.

LOG−ODD scores were calculated according to Zhang and Marr [26] using the GeneId dataset and randomly extracted splice sites as a comparison. The scoring function is defined as:

$$S_i(X) = \log_2 \frac{P_i(X)}{Q(X)}$$

$P_i(X)$ is the frequency of finding X at position i that is equal to $C_i(X)/D_i$. The normalization D_i is the sum of the counts $C_i(X)$ over X (=A,C,G,T). We used Q(X)=1/4 for all X as the random background frequency. The score for a splice site is the sum of the scores for each individual nucleotide.

RESULTS AND DISCUSSION

Different classes of alternatively spliced exons in neurons

The different classes of alternatively spliced exons are shown in Table 1. They were arranged according to their gene structure, gene expression and splicing pattern. The splicing pattern is schematically indicated on top of each class. Exons that introduce known regulatory elements like phosphorylation sites, stop codons or frameshifts are listed at the end of each list. The reading frame is indicated by a '@'. The regulation of the alternative splicing, the expression pattern and the experimental techniques used to analyse the alternative exons are included if such information was available in the literature.

Splice site analysis

The nucleotide composition of splice sites surrounding alternatively spliced exons has been shown to be important for their alternative use [27]. The deviation of splice sites from the consensus sequence [28] seems to decrease binding of splicing factors around the alternatively spliced exon and to limit its use. Mutations in the 5′ splice site that interfere with U1 snRNA binding have been shown to decrease the usage of exons [29, 30]. The composition of the 3′ splice site [31] and the branch point has been shown to be important. However, the splice sites of alternative exons do not always deviate from the consensus. For example, the splice sites surroundng the exons coding for substance P [16], sexlethal and the Drosophila P element [8] match the consensus sequence.

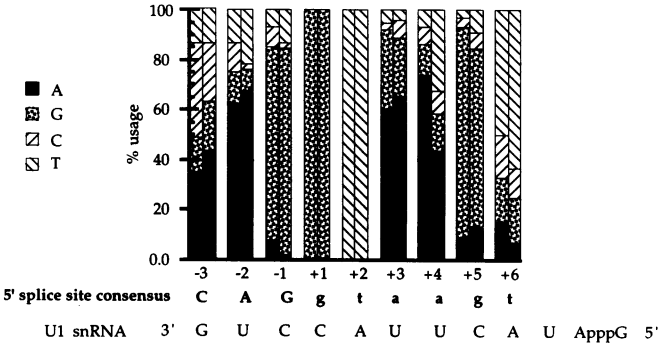


Figure 1. Nucleotide usage at the 5′ splice site. The percent nucleotide usage of constitutively (left) and neuron specific alternatively spliced exons (right) is pairwise compared. The U1 sequence and the vertebrate consensus splice site sequence are shown at the bottom. The different nucleotides are indicated by different patterns, as indicated in the figure.

General 5′ splice site composition

The 5′ splice site consensus sequence reflects base pairing with U1 snRNA. A comparison of 5′ splice sites from common and neuron specific alternatively spliced exons is shown in Figure 1. On average, neuron specific 5′ splice sites deviate most from the consensus at the +3 and −4 position, where the consensus nucleotide is present 40% less often than in constitutive exons. In position +2, +1, and −3 use of the consensus nucleotide is increased by 8%, at the position −5 it is decreased by 16% and at −6 it is increased by 26%. Addition of these percentages shows that neuron specific 5′ splice sites overall use 49% fewer consensus nucleotides complementary to U1 snRNA. However, this deviation is not equally distributed. Most deviation takes place at two positions, +3 (consensus: C) and −4 (consensus: A). Whether this uneven distribution has functional significance has

to be determined. The nucleotide at the −4 position has been postulated to interact with A_{49} of the U6 snRNA in a late step in splicing [32, 33]. Compared to constitutive 5′ splice sites, alternatively spliced neuronal 5′ splice sites have fewer A, but more U at this position, thus on average binding of their 5′ splice sites with U6 snRNA might be facilitated. It is interesting to note that the consensus nucleotide at the −4 position in yeast is also U, but the significance of this similarity is unclear.

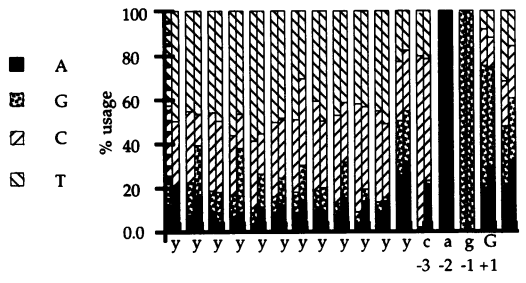


Figure 2. Nucleotide usage at the 3′ splice site. The percent nucleotide usage of constitutively (left) and neuron specific alternatively spliced exons (right) is pairwise compared. The vertebrate consensus sequence is indicated at the bottom, exon sequences are in capital letters. Note the use of A in alternativly spliced exons at the −3 position. The different nucleotides are indicated using the same patterns as in Figure 1.

General 3′ splice site composition

The comparison of the 3′ splice sites from neuron specific alternatively spliced exons and common exons reveals differences at the −3 position (Figure 2). Twenty one percent of all neuron-specific exons use an A at this position, compared to only 4% in constitutively used 3′ splice sites. The reason why a pyrimidine is conserved at the −3 position is not clear. However, it has been demonstrated that a C→A mutation at this position reduces splicing efficiency by 70% [30]. In addition, in each but the −14 position, neuron specific 3′ splice sites have a higher purine content when compared with constitutive 3′ splice sites.

Evaluation of splice sites using LOG−ODD scores

In order to assess the splice site quality, we calculated LOG−ODD scores for each splice site. The LOG−ODD scores express the coincidence of a splice site with the consensus sequence; a higher coincidence generates a higher score. We first calculated a score for each alternative splice site and compared the distribution of individual scores with constitutively spliced exons. Since it has been postulated that the splice sites surrounding an exon define its borders in a concerted way [34], we then calculated the LOG−ODD scores for the splice sites

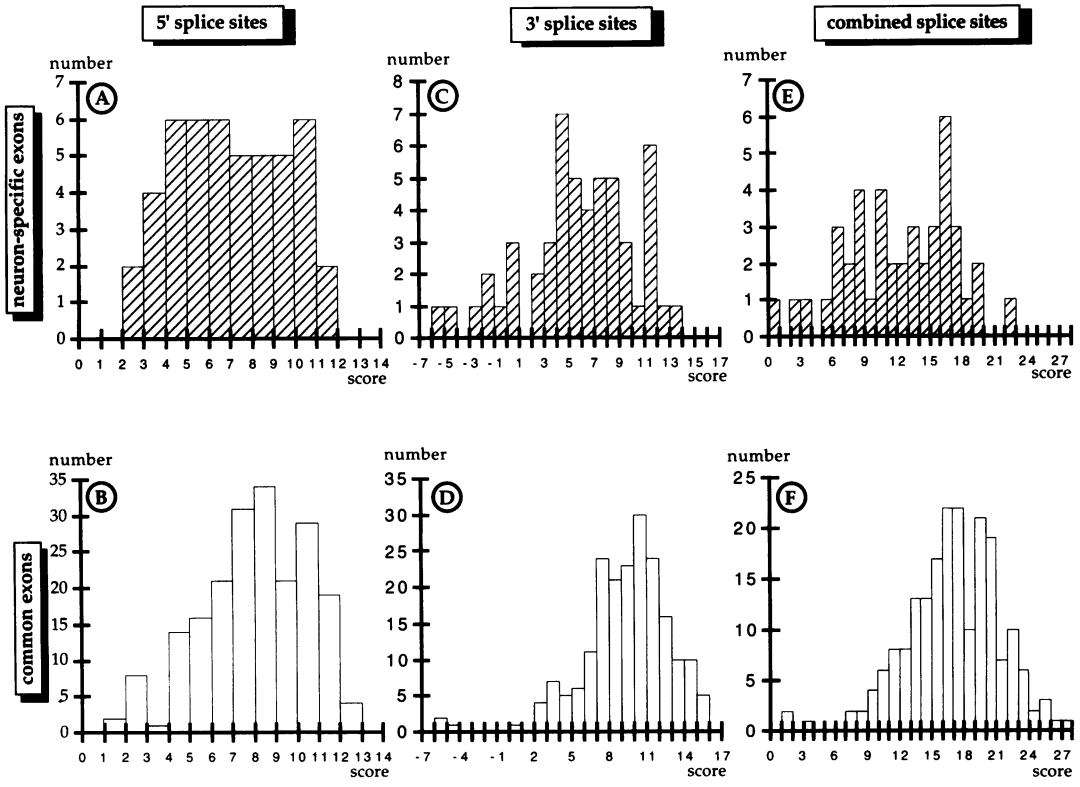


Figure 3. Distribution of splice sites scores in neuron specific and consitutivly spliced vertebrate exons. The scores are plotted on the x-axis, the higher the score the better is the match to the consensus sequence. The number of splice sites that accompany a certain score are plotted on the y-axis. Neuron-specific exons are shaded. **A.** Distribution of neuron-specific 5′ splice sites. **B.** Distribution of common 5′ splice sites. A perfect match to U1 would have a score of 12.2. The mean of the distribution is 7.1 for neuron specific exons and 8.0 for constitutively spliced exons. **C.** Distribution of neuron-specific 3′ splice sites. **D.** Distribution of common 3′ splice sites. A 'perfect' 3′ splice site $(u)_{11}$cagG would have a score of 15.6. The mean of the distribution is 5.7 for neuron specific exons and 9.4 for constitutively spliced exons. **E.** Distribution of combined scores of 5′ and 3′ splice sites that surround an neuron-specific exon **F.** Distribution of combined scores of 5′ and 3′ splice sites that surround an common exon. An exon surrounded by a 'perfect' 3′ and 5′ splice site would have a score of 27.8. The mean of the distribution is 12.2 for neuron specific exons and 16.9 for constitutively spliced exons.

surrounding one exon. Compared to the control splice sites, the distribution of alternative donor and acceptor splice sites is broader and the mean of the distribution is at a lower score (Figure 3, A and B). This could indicate the presence of two subclasses of splice sites in alternatively spliced exons, with one subclass having the splice sites in consensus and the other subclass having sub-optimal splice sites. When the splice sites surrounding one individual exon are considered, the presence of two subclasses becomes more apparent (Figure 3, E and F). One group of alternatively spliced exons has splice sites that are sub-optimal, whereas another group has splice sites that score similar to the splice sites of constitutively spliced exons. This could mean that the first group of exons is most likely regulated by their splice site quality, which is in agreement with the exon definition model [34]. Skipping of these exons is the most likely default mechanism. The second group is most likely regulated by other elements like steric hindrance [15], secondary structures [16] or factors that bind to flanking intron sequences [35].

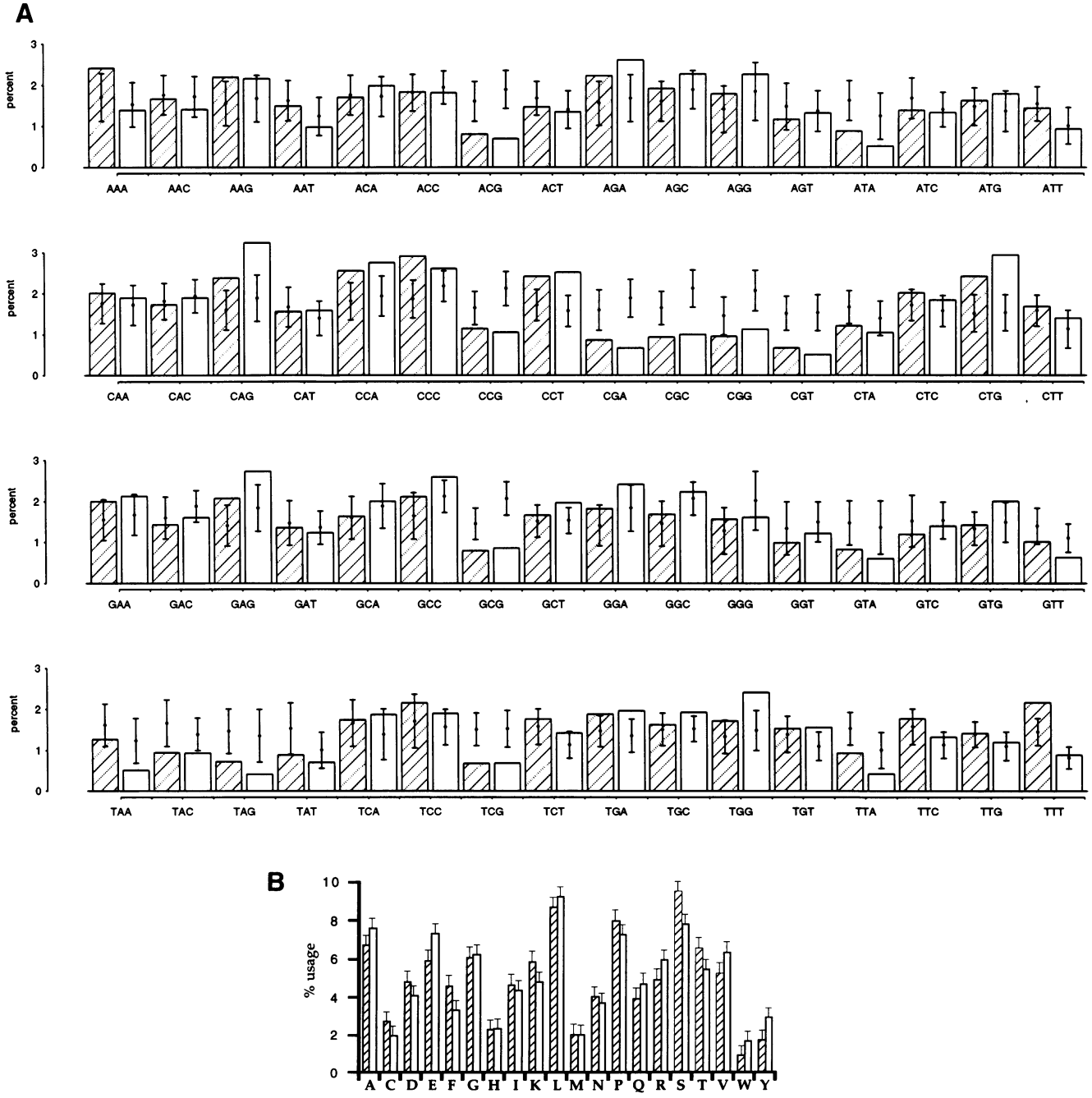


Figure 4. Trinucleotide and amino acid distribution in neuron specific (shaded) and constitutively spliced exons (open). **A.** Distribution of overlapping 3-tuples in alternatively and constitutively spliced exons. The actual nucleotide distribution of alternativly and constitutivly exons was used to calculate the random nucleotide distribution by random shuffling, the means and the double standard deviations of these random samples are plotted as dots and error bars. Columns indicate the actual percent usage of each 3-tuple. **B.** Distribution of amino acids in alternatively and constitutively spliced exons. The percent usage of each amino acid is indicated. The error bars indicate the standard deviation.

Nucleotide composition of alternative spliced exons and possible motifs

We analysed the nucleotide composition of the alternatively spliced exons to assess its possible role in exon usage. Overall, alternatively spliced exons are more AU-rich (26%A, 27% C, 24%G, 23% U) than common exons (25%A, 28% C, 27%G, 20% U). The p-values [36] calculated for the differences of the A, C, G, and U values are 0.015, 0.106, 2.97×10^{-12} and 4.68×10^{-11}, respectively. Therefore, the null hypothesis that the nucleotide composition in constitutively and alternativly spliced exons are the same should be rejected at the 0.05 significance level for all nucleotides except C. We conclude from this statistical analysis that the differences in nucleotide composition are significant.

Since several groups reported the involvement of exon motifs in recognition of alternatively spliced exons [13, 37–47] we analysed the neuron specific exon database for k-tuple frequencies according to Claverie *et al.* [48]. The overlapping 3-tuple distributions in both alternatively and constitutively spliced exons are plotted in Figure 4, A. The expected frequencies and the dispersions for random sequences with the same nucleotide compositions were calculated by randomizing each data set and are indicated as error bars in Figure 4, A. The general feature for all exons is the rare use of TA and CG dinucleotides as shown by the deviation below the random expectations, possibly to avoid termination and methylation. Assuming that the nucleotides assemble independently of each other, most of the differences in 3-tuple frequencies between the two exon data sets can be explained by the single nucleotide composition, because the 3-tuple frequencies follow the trend of the random expectations. However, some of the major differences cannot simply be attributed the single nucleotide composition, for example the relative high frequency of trinucleotides AAA and TTT in alternatively spliced exons cannot be explained by the single nucleotide composition and by the amino acid composition of the alternativly spliced exons (Figure 4, B).

In common exons, the trinucleotides CAG, CTG, AGA, TGG and GAG are more frequent than what would be expected in a random assembly. Their high frequency cannot be explained by the amino acid composition of the common exons (Figure 4, B), because only the amino acids F, S, W, Y could contribute to a 3-tuple frequency difference but except F these differences are not correlated to the different trinucleotide distribution. We therefore assume that constraints that lead to the different 3-tuple distribution are due to regulatory requirements on the RNA level. We furthermore conclude that the different 3-tuple composition of alternatively and constitutively spliced exons might have regulatory significance in splicing.

The high frequency of certain trinucleotides probably represents the general characteristics of common exons. In order to see how these 3-tuples are distributed in alternatively spliced exons, we computed the 3-tuple frequency per sequence for the neuron specific exons (each 3-tuple counts at most once in each exon), CAG and AGA were found to be the most frequent, with more than 89% of the alternatively spliced exons containing either CAG or AGA (data not shown).

In order to find motifs common in alternatively spliced exons, we used the RTide program which was designed to search short motifs in multi-sequences [49]. We were unable to identify a motif in the exon sequences or in subset of these sequences. However, our RTide analysis indicated that CAGA might be part of possible motifs in alternatively spliced exons.

The AU rich nucleotide composition and the distribution of tri and tetranucleotides in alternatively spliced exons is in contrast to several AG rich sequence motifs that have been described as necessary for alternative exon usage [38–40, 42, 43, 45–47]. It is tempting to speculate that the AG rich motifs that are in an AU rich context of the alternatively spliced exons serve as signals for the splicing machinery, presumably through binding to an hnRNP. In the light of our analysis, the mutation of these motifs leads to skipping of the alternative exon, because different or no trans factors are now binding to the mutant exon and make it recognizable to the splicing machinery.

Since rapid progress is being made in sequencing and identifying neuron specific exons, we hope that in future updates of this sequence comparison putative motifs will become more clear.

Update

Since we are planning to update this compilation in the future, we would be thankful for the communication of new or here omitted neuron specific exons. Furthermore, the sequences can be obtained electronically either from stamm@cshl.org or by anonymous ftp from phage.cshl.org in the /pub/science/alt_exon directory.

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