

Understanding Neurodevelopmental Disorders: The Promise of Regulatory Variation in the 3'UTRome

Supplemental Information

SUPPLEMENTARY DATA

Systematic review of literature

In order to identify NDD associated variants in 3'UTRs we performed a literature search with a combination of following Mesh Terms. In general, it was attempted to combine terms describing individual NDDs (ADHD, SZ, ASD, ID) with terms for next-generation sequencing (RNA-seq, WES, WGS) or GWAS and 3'UTRS. For a general search of variants in NDDs, the terms 'Non-coding RNA', 'Neurodevelopmental Disorder', '3'UTR' and 'Brain' were combined. The following paragraph shows all used combinations.

In total, 824 articles were obtained from the search. 41 of them were used to identify disease associated variants in 3'UTRs. The search was conducted on 08-08-2016 (specific disorders), 25-04-2016 (3'UTRs in general) and 01-11-2016 (disease + 3'UTR) using PubMed.

Variants that are located to 3'UTRs and that were correlated to a disorder were considered candidates for Table 1. The variation in study design, sample size and statistical method prevented a common statistical test for the variants. We therefore took every variant into account that was considered 'associated', 'linked' or 'correlated' by its corresponding study. The list was complemented with variants that were identified by studies in our own lab (ARHGEF39, BTN2A1, CENPJ, MTMR3) and variants that were found using the miRdSNP database. We extracted those SNPs from miRdSNP that were located in 20 bp distance of a MBS and also associated to ADHD, SZ or ASD. 11 variants in 10 genes were found this way.

For ADHD:

Search from **01-11-16:**

[ADHD] AND [3'UTRs]

Found 125 articles

Search from **08-08-16:**

[ADHD] AND [Next Generation Sequencing] AND [3'UTR]

[ADHD] AND [GWAS] AND [3'UTR].

Found 12 articles

For ASD:

Search from **01-11-16:**

[ASD] AND [3'UTRs]

Found 66 articles

Search from **08-08-16:**

[ASD] AND [Next Generation Sequencing] AND [3'UTR]

[ASD] AND [GWAS] AND [3'UTR].

Found 8 articles

Search from **01-11-16**:

[ID] AND [3'UTRs]

Found 180 articles

Search from **08-08-16**:

[ID] AND [Next Generation Sequencing] AND [3'UTR]

[ID] AND [GWAS] AND [3'UTR].

Found 18 articles

For SZ:

Search from **01-11-16**:

[Schizophrenia] AND [3'UTRs]

Found 152 articles

[Schizophrenia] AND [Next Generation Sequencing] AND [3'UTR]

[Schizophrenia] AND [GWAS] AND [3'UTR].

Found 14 articles

For 3'UTRs in general:

Search from 25-04-16:

[Non-coding RNA] AND [Neurodevelopmental Disorder]

[3UTR AND Brain AND Mutation]

Found 249 articles

Supplementary Table S1: All 3'UTR variants identified via systematic review

Disorder	Gene	Variant	Genomic Coordinates (hg38)	RBPMap		Predicted MBS (miRSNP)	Reference	Known Candidate gene?	Functionally Validated?
				Input Coordinates for RBPMap	Outcome RBPs				
ADHD	SLC6A3 (DAT1)	rs28363170	chr5:1393747	chr5:1393737-1393757:-	ENOX, MBNL1, SRSF1, SRSF5	No prediction ¹	(1, 2)	Yes	Yes (3)
	CLOCK	rs1801260	chr4:55435202	chr4:55435192-55435212:--	DAZAP1, TRA2B	NA ³	(4, 5)	Yes	Yes
	SNAP-25	rs3746544	chr20:10306436	chr20:10306426-10306446:-	FXR1, PABPC, RBM46, SNRNP70, SRSF1, SRSF5, SRSF7, TRA2B, YBX1	hsa-miR-3617, hsa-miR-3913-3p, hsa-miR-641	(6)	Yes	
		rs1051312	chr20:10306440	chr20:10306430-10306450:+	HuR, MATR3, PTBP1, SRSF1, SRSF3, SRSF5, TRA2B	hsa-miR-3646, hsa-miR-3664-3p, hsa-miR-510	(6-8)	Yes	
	MECP2	*c.1558insA	chrX:154028729	chrX:154028719-154028739:-	SRSF5	NA ²	(9)	Yes	
	SLC9A9	rs1046706	chr3:143266258	chr3:143266248-143266268:+	DAZAP1, MSI1, PCBP3	NA ³	(10)	Yes	
	DBH	rs129882	chr9:133658547	chr9:133658537-133658557:+	MBNL1, SRSF5, SRSF7	NA ³	(11)	Yes	Yes
		rs1611115	chr9:133635393	chr9:133635383-	FMR1, HNRNPH1,	NA ³	(11)	Yes	Yes

				133635403:+	HNRNPH2,LIN28A, SRSF1,SRSF10, SRSF2,SRSF5, TARDBP				
	<i>MTHFR</i>	rs4846049	chr1:11790308	chr1:11790298- 11790318:+	SRSF2, TRA2B	NA ³	(12)	Yes	Yes (13)
Schizophrenia	<i>PTPRA</i>	174620_174623 het_dupTGAT	No coordinates available	NA	NA	NA ²	(14)	Yes	
	<i>GZF1</i>	rs7988	chr20:23372048	chr20:23372038- 23372058:+	HNRNPL, HNRPLL, IGF2BP2, IGFBP3, KHDRBS2, KHDRBS3, PABPC1, PABPC4, PUM2, QKI, RBM46, RBMS3, SART3, SRSF3, SRSF5, ZCRB1	hsa-miR-3686	(7, 15)	No	
	<i>CPLX2</i>	rs3822674	chr5:175880253	chr5:175880243- 175880263:-	CPEB2, CPEB4, HNRNPC, HNRNPCL1, MBNL1, MSI1, PTBP1, SRSF1, SRSF3, SRSF5, TUT1	hsa-miR-4287, hsa-miR-4685-3p, a-miR-498	(7, 16)	Yes	Yes
		rs56934064	chr5:175880290	chr5:175880280- 175880300:+	HNRNPA1, HNRNPA1L2, HNRNPA2B1, HNRNPF, HNRNPH2	NA ³	(16)	Yes	
	<i>EFNB2</i>	rs9520087	chr13:106491972	chr13:106491962- 106491982:+	BRUNOL4, BRUNOL5, MBNL1, PTBP1, SRSF3, TARDBP	hsa-miR-155-3p, hsa-miR-4999-5p	(7, 17)	Yes	
		rs550067317	chr13:106491980	chr13:106491970- 106491990:+	BRUNOL5, PTBP1, SRSF2, SRSF3, TARDBP	NA ³	(18)	Yes	Yes
	<i>DISC1/ DISC2</i>	rs6675281	chr1:231818355	chr1:231818345- 231818365:+	NOVA1, PABPC3, SRF3, SRSF5	hsa-miR-1294, hsa-miR-4710	(7, 19)	Yes	
	<i>DISC1</i>	rs821616	chr1:232008852	chr1:232008842- 232008862:-	CUG-BP, MBNL1, SRSF1, SRSF5	hsa-miR-1243, hsa-miR-4423-3p	(7, 20)	Yes	
		rs3737597	Chr1:232037092	chr1:232037082- 232037102:-	FXR1, HNRNPH1, PABPC3, PABPC5, PCBP1, PCBP3, RBM45, SRSF3, SRSF7, TRA2B	NA ³	(21)	Yes	
	<i>OLIG2</i>	rs1059004	chr21:33028155	chr21:33028145- 33028165:+	HNRNPK, PCBP1, SRSF2, SRSF3, SRSF5	hsa-miR-323a-5p, hsa-miR-3689d	(7, 22)	Yes	
		rs13046814	chr21:33029069	chr21:33029059- 33029079:+	FUS, PCBP2, SRSF3, SRSF5	hsa-miR-2277-5p, hsa-miR-4639-3p, hsa-miR-744-5p	(7, 22)	Yes	
	<i>AMACR</i>	rs2278008	chr5:33989413	chr5:33989403- 33989423:+	HNRPLL, MATR3, MBNL1, PTBP1, SRSF3, SRSF5	hsa-miR-942	(7, 23)	Yes	
	<i>NFKBIA</i>	rs8904	chr14:35402011	chr14:35402001- 35402021:-	SRSF9, TARDBP, ZC3H10	hsa-miR-3121-5p	(7, 15)	Yes	
<i>LIF</i>	rs737812	chr22:30243121	chr22:30243111-	CNOT4, PABPN1, PCBP1,	hsa-miR-373-5p,	(7, 24)	Yes		

				30243131:+	PCBP2, PTBP1, RBM6, SRSF3	hsa-miR-499b-5p, hsa-miR-616-5p, hsa-miR-617			
		rs929271	chr22:30242237	chr22:30242227-30242247:-	BRUNOL6,CUG-BP,HNRNPF, HNRNPU,MBNL1, PTBP1,SRSF2, SRSF5,TARDBP	NA ³	(24)	Yes	
	<i>DCLK1</i>	rs9545297	chr13:35767531	chr13:35767521-35767541:+	BRUNOL6, CUG-BP, HNRNPU, HNRPLL, MBNL1, RBM41, SRSF3, TARDBP, TRA2B	NA ³	(7, 25)	Yes	
	<i>PLA2G12A</i>	rs3087494	chr4:109710465	chr4:109710455-109710475:+	CPEB2, CPEB4, HNRNPA1L2, HNRNPCL1, HuR, MATR3, PTBP1, RALY, SRSF3, TIA1, TRA2B, U2AF2, ZC3H14	NA ³	(26)	Yes	
	<i>RGS4</i>	rs10759	chr1:163076561	chr1:163076551-163076571:-	IGF2BP2, SRSF3	NA ³	(27)	Yes	Yes
	<i>COMT</i>	rs165599	chr22:19969008	chr22:19968998-19969018:+	A1CF, KHDRBS2, KHDRBS3, MSI1, PABPC5, PUM2, RBM42, RBM46, RBMS3, ZCRB1	NA ³	(28)	Yes	
	<i>CTLA4</i>	rs3087243	chr2:203874196	chr2:203874186-203874206:+	KHDRBS1, QKI, RBMS1, RBMS3, SRSF3	NA ³	(29)	Yes	
Specific Language Disorder (SLI)	<i>ARHGEF39</i>	rs72727021	chr9:35661946	chr9:35661936-35661956:+	SRSF3, SRSF5	NA ³	(30)	No	Yes
	<i>BTN2A1</i>	c.277 G>C	chr6:26468826	chr6:26468816-26468836:+	CUG-BP, PABPC5, PAPN1, RBM24, TARDBP, TRA2B	NA ²	(30)	No	
	<i>CENPJ</i>	c.16G>T	chr13:24883161	chr13:24883151-24883171:-	QKI, SRSF1, SRSF3, TRA2B	NA ²	(30)	No	
	<i>MTMR3</i>	c.70C>T	chr22:30025871	chr22:30025861-30025881:+	CNOT4, ENOX1	NA ²	(30)	No	
Language and reading impairments	<i>CCDC136</i>	rs59197085	chr7:128820702	chr7:128820692-128820712:+	PTBP1, SRSF3, SRSF5	No prediction ¹	(31)	No	
	<i>DYX1C1</i>	rs57809907	chr15:55430684	chr15:55430674-55430694:+	A1CF, HuR, MBNL1, PTBP1, SRSF3, ZC3H14, ZCRB1, ZNF638	No prediction ¹	(32)	Yes	
Tourette's Syndrome	<i>SLITRK1</i>	Var321 (mutation)	chr13:83878728	chr13:83878718-83878738:+	SRSF3	NA ²	(33)	Yes	Yes
Autism Spectrum Disorder (ASD)	<i>HLA-G</i>	14 bp indel	Chr6:1093208	chr6:1093198-1093218:+	SRSF5	NA ²	(34)	Yes	
	<i>AFF2</i>	ChrX:148.076.068[C>T]	chrX:148994538	chrX:148994528-148994548:+	HNRNPA1, HNRNPA1L2, HNRNPA2B1, MBNL1, SRSF3, SRSF5,	NA ²	(35)	Yes	Yes

		ChrX:148075200[T>C]	chrX:148993670	chrX:148993660-148993680:+	ZCRB1 HNRNPL, HNRPLL, RBM41, RBMS1, RBMS3, SRSF3, SRSF5, TUT1	NA ²	(35)	Yes	
	<i>STX1A</i>	rs867500	chr7:73700110	chr7:73700100-73700120:+	HNRNPH2, RBM5, SRSF1, SRSF9, TARDBP	hsa-miR-1204	(36)	Yes	Yes
	<i>APC</i>	rs1804197	chr5:112844212	chr5:112844202-112844222:+	A1CF, FXR1, KHDRBS1, KHDRBS2, KHDRBS3, PABPC1, PABPC3, PABPC4, PABPC5, PABPN1, SART3, ZCRB1	hsa-miR-335-3p, hsa-miR-4282	(7, 37)	No	
	<i>NLGN4X</i>	chrX:5818136	chrX:5890095	chrX:5890085-5890105:-	CNOT4, KHDRBS1, KHDRBS2, KHDRBS3, PUM2, RBMS1, RBMS3, SRSF3	NA ²	(38)	Yes	
		chrX:5820149-50	chrX:5892108	chrX:5892098-5892118:-	CPEB4, MBNL1, SRSF2, TIA1, TRA2B, U2AF2	NA ²	(38)	Yes	
	<i>SLC6A4</i>	HTT-3'UTR-SNP 1461*139 G->A	No coordinates available chrX:154030343	NA chrX:154030333-154030353:-	NA HNRNPK, HNRPLL, IGF2BP2, PABPC3, RBM46, SNRPA, YBX1	NA ²	(39)	Yes	
	<i>MECP2</i>	c.1832G>C	chrX:154030065	chrX:154030055-154030075:-	CUG-BP, FMR1, FXR2, HNRPLL, MBNL1, SRSF2, SRSF7	NA ²	(41)	Yes	Yes
		c.2015G>A	chrX:154029882	chrX:154029872-154029892:-	CNOT4, ENOX1, HNRNPA1, HNRNPH1, HNRNPH2, PABPN1, RBM24, SRSF10, SRSF2, TARDBP, TRA2A	NA ²	(41)	Yes	Yes
		c.4017T>A	chrX:154027880	chrX:154027870-154027890:-	HNRNPK, HNRPLL, RBM42, RBM46, SRSF2, SRSF3	NA ²	(41)	Yes	Yes
		c.4417G>A	chrX:154027480	chrX:154027470-154027490:-	NOVA1, SRSF5, SRSF7	NA ²	(41)	Yes	Yes
		c.1655G>A	chrX:154030242	chrX:154030232-154030252:-	CPEB2, CPEB4, HNRNPC, HNRNPCL1, HuR, KHDRBS2, KHDRBS3, MBNL1, PABPC3, PTBP1, RALY, RBM41, SRSF3, SRSF5, TIA1, U2AF2, ZC3H14	NA ²	(41)	Yes	
		c.2322T>G	chrX:154029575	chrX:154029565-154029749:-	DAZAP1, ENOX1, ESRP2, FMR1, FXR1, G3BP2, HNRNPA1, HNRNPA2B1,	NA ²	(41)	Yes	

				HNRNPF, HNRNPH1, HNRNPH2, MBNL1, PTBP1, RBM28, RBM42, RBM5, SAMD4A, SRSF1, SRSF2, SRSF3, SRSF5, SRSF7, SRSF9, TARDBP				
c.2829C>A	chrX:154029068	chrX:154029058-154029078:-	MBNL1, PCBP1, PCBP2, PTBP1, SRSF2, SRSF3, SRSF5	NA ²	(41)	Yes		
c.3198G>A	chrX:154028699	chrX:154028852-154028872:-	MBNL1, PCBP1, PCBP3, PTBP1, SRSF3, SRSF5	NA ²	(41)	Yes		
c.6037A>C	chrX:154025860	chrX:154025850-154025870:-	HNRNPA1L2, HNRNPA2B, MBNL1, PCBP2, SRSF5	NA ²	(41)	Yes		
c.6948ins(AT)	chrX:154024949	chrX:154024939:-154024959:-	A1CF, CPEB2, CPEB4, CUG-BP, DAZAP1, HNRNPC, HNRNPCL1, HuR, MBNL1, PCBP3, RALY, RBM41, SFPO, SRSF2, SRSF3, TIA1, TRA2B, U2AF2, ZC3H14	NA ²	(41)	Yes		
c.9209C>T	chrX:154022688	chrX: 154022678-154022698:-	CUG-BP, HNRNPF, PTBP1, RBM38, SRSF1, SRSF5, TARDBP, TRA2B	NA ²	(41)	Yes		
c.9317A>C	chrX:154022580	chrX: 154022570-154022590:-	HNRNPK, PCBP1, PCBP2, PCBP3, PTBP1, SRSF3	NA ²	(41)	Yes		
T>C c.6809	chrX:154025007	chrX:154024997-154025017:-	MBNL1, SRSF3, TARDBP	NA ²	(9)	Yes		
G>C c.1638	chrX:154028649	chrX:154028639-154028659:-	CUG-BP, HNRNPA1, HNRNPA1L2, MBNL1, RBM28, ZC3H10	NA ²	(9)	Yes		
c.1470G > A	chrX:154030427	chrX:154030417-154030437:-	HNRNPK, HNRNPL, SRSF7, YBX1	NA ²	(41)	Yes		
c.2005G > A	chrX:154029892	chrX:154029882-154029902:-	CNOT4, ENOX1, FMR1, FXR2, HNRNPA1, HNRNPA2B1, HNRNPH2, RBM24, SRSF2, TARDBP	NA ²	(41)	Yes		

		c.2228G > T	chrX:154029669	chrX:154029659-154029679:-	ENOX1, FMR1, FXR1, SRSF3, SRSF7	NA ²	(41)	Yes	
		c.4118G > A	chrX:154027779	chrX:154027769-154027789:-	ESRP2, HNRNPA1, HNRNPA2B1, HNRNPF, HNRNPH1, HNRNPH2, PABPN1, SRSF2, TRA2A	NA ²	(41)	Yes	
		c.4167G > A	chrX:154027730	chrX:154027720-154027740:-	CUG-BP, MBNL1, PTBP1, SRSF2, SRSF3	NA ²	(41)	Yes	
		c.5119C > T	chrX:154026778	chrX:154026768-154026788:-	CUG-BP, HNRNPA1, MBNL1, SRSF2, SRSF5	NA ²	(41)	Yes	
		c.5339G > C	chrX:154026558	chrX:154026548-154026568:-	SNRPA	NA ²	(41)	Yes	
	OXTR	rs7632287	chr3:8749760	chr3:8749750-8749770:+	RBM41, SNRPA, SRSF3, SRSF7	NA ³	(42)	Yes	
		rs237884	chr3:8751899	chr3:8751889-8751909:+	KHDRBS3, MBNL1, PUM2, SRSF5	NA ³	(42)	Yes	
Intellectual Disability	CDK5RI	c.1005G>A	Chr17:32488404	chr17:32488394-32488414:+	MBNL1, PTBP1, SRSF2, SRSF5	NA ²	(43)	Yes	
		c.1043G>A	Chr17:32488442	chr17:32488432-32488452:+	CUG-BP, MBNL1, SRSF2, TUT1	NA ²	(43)	Yes	
		c.2160C>T	chr17:32489559	chr17:32489549-32489569:+	HuR, KHDRBS3, PTBP1, PUM2, RBMS1, SRSF3, TRA2B	NA ²	(43)	Yes	
		c.2254C>G	chr17:32489653	chr17:32489643-32489663:+	CUG-BP, MBNL1, SRSF1, SRSF2	NA ²	(43)	Yes	
		c.3452G>A	chr17:32490851	chr17: 32490841-32490861:+	CPEB2, CPEB4, HNRNPC, HNRNPCL1, HuR, MATR3, MBNL1, PTBP1, RALY, SRSF3, SRSF5, TIA1, U2AF2, ZC3H14, ZNF638	NA ²	(43)	Yes	
		c.*71 G>A	chr17:32488916	chr17:32488906-32488926:+	CUG-BP,HNRNPA1, HNRNPA1L2, HNRNPA2B1, HNRNPF, SRSF2, SRSF5, TARDBP, TIA1	NA ²	(44)	Yes	
		rs8192474	chr17:32488663	chr17:32488653-32488673:+	NOVA1, PCBP1, PCBP2, PCBP3, PTBP1, SRSF3, SRSF5	hsa-miR-1915-3p, hsa-miR-4441, hsa-miR-548ac	(44)	Yes	
		rs138054348	chr17:32490069	chr17:32490059-32490079:+	CUG-BP, HNRNPF, SRSF1, SRSF9	hsa-miR-4691-3p, hsa-miR-766-3p	(44)	Yes	
		rs735555	chr17:32490432	chr17:32490422-32490442:+	BRUNOL4, BRUNOL5, CPEB4, HuR, MBNL1, PTBP1, RBM38, RBM6, SRSF2, SRSF3, TARDBP,	NA ²	(44)	Yes	

				ZC3H14						
	rs115744590	chr17:32490719	chr17:32490709-32490729:+	CPEB4, CUG-BP, MATR3, MBNL1, PTBP1, RBM41, SRSF1, SRSF2, SRSF3, SRSF5, TIA1, TRA2B, U2AF2, ZC3H14	hsa-miR-338-5p, hsa-miR-3680-3p	(44)	Yes			
	c.*397C>G	Chr17:32489242	chr17:32489232-32489252:+	A1CF, CUG-BP, HNRNPM, HuR, MBNL1, PTBP1, SFPO	NA ³	(44)	Yes	Yes		
	c.*649_*659del	Chr17:32489494	chr17:32489484-32489504:+	CUG-BP, MBNL1, SRSF2, SRSF3	NA ³	(44)	Yes			
	c.*1904_*1905del	Chr17:32490749	chr17:32490739-32490759:+	BRUNOL4, BRUNOL5, CPEB4, HNRNPC, HNRNPCL1, MATR3, PTBP1, RALY, RBM24, RBM38, SRSF1, SRSF9, TARDBP, TIA1	NA ³	(44)	Yes	Yes		
	c.*2099_*2101del	Chr17:32490944	chr17:32490934-32490954:+	KHDRBS1, KHDRBS2, KHDRBS3, NOVA1, PABPC1, PABPC4, PABPC5, PABPN1, SART3, TRA2B	NA ³	(44)	Yes	Yes		
	<i>CDK5</i>	rs9278	chr7:151053893	chr7:151053883-151053903:-	BRUNOL6, HNRNPF, HNRNPH2, MBNL1, SFPO	hsa-miR-3064-5p, hsa-miR-3620, hsa-miR-3944-3p, hsa-miR-4269	(44)	Yes		
	<i>FMR1</i>	c.*746T>C	chrX:147949590	chrX:147949580-147949600:+	BRUNOL4, BRUNOL5, BRUNOL6, CPEB2, CPEB4, HNRNPC, HNRNPCL1, HNRNPM, HNRNPU, HuR, MBNL1, RALY, SRSF2, TIA1, TRA2B, U2AF2, ZC3H14, ZNF638	NA ²	(45, 46)	Yes	Yes	
		c.*1867G>A	chrX:147950711	chrX:147950701-147950721:+	DAZAP1, KHDRBS1, KHDRBS3, MSI1, PABPC1, PABPC5, RBMS1, RBMS3, SART3, SRSF2, TRA2B	NA ²	(45)	Yes		
		c.*23T>C	chrX:147948867	chrX:147948857-147948877:+	A1CF, PCBP3, PTBP1, RBM41, RBMS1, RBMS3, SRSF3, TUT1, U2AF2	NA ²	(47)	Yes		
		c.*2035C>T	chrX:147950879	chrX:147950869-147950889:+	CUG-BP, MBNL1, PTBP1, RBM42, SRSF3	NA ²	(47)	Yes		
		10 unnamed variants	No coordinates available	NA	NA	(47)	Yes			
	<i>MECP2</i>	1461*93G > A	chrX:154030436	chrX:154030426-	HNRNPK, SRSF3, YBX1	NA ²	(48)	Yes		

				154030446:-					
Rett-Syndrome	<i>MECP2</i>	c.1461+98insA	chrX:154030436	chrX:154030426-154030446:-	HNRNPK,SRSF3, YBX1	NA ²	(49, 50)	Yes	
		c.9961C>G	chrX:154021936	chrX: 154021926-154021946:-	A1CF, HNRNPC, HNRNPCL1, KHDRBS3, PABPC5, QKI, RBMS3, ZC3H14, ZCRB1	NA ²	(49)	Yes	
		c.9964delC	chrX:154021933	chrX:154021923-154021943:-	A1CF, HNRNPC, HNRNPCL1, KHDRBS3, PABPC5, QKI, RBMS3, ZC3H14, ZCRB1	NA ²	(49)	Yes	
		c.1461+9G>A	chrX:154030436	chrX:154030426-154030446:-	HNRNPK,SRSF3, YBX1	NA ²	(49)	Yes	
		c.2595G>A	chrX:154029302	chrX: 154029292-154029312:-	SRSF1, SRSF5	NA ²	(49)	Yes	
		c.1461+92C>G	chrX:154030436	chrX:154030426-154030446:-	HNRNPK,SRSF3, YBX1	NA ²	(50)	Yes	
Anxiety and Depression	<i>MAP2K5</i>	rs41305272	chr15:67807105	chr15:67807095-67807115:+	CUG-BP, HNRNPA1, MBNL1, QKI, TARDBP, TRA2B, ZCRB1	NA ³	(51, 52)	Yes	
	<i>P2RX7</i>	rs1653625	chr12:121185082	chr12:121185072-121185092:+	IGF2BP2, IGF2BP3, KHDRBS1, KHDRBS2, KHDRBS3, PABPC1, PABPC3, PABPC4, PABPC5, PABPN1, SART3	NA ³	(53)	Yes	

¹The SNP was not predicted to affect an existing MBS

²The variant was not reported as SNP with rs-identifier. As such it was not usable in the miRSNP program

³Not possible as MiRSNP webpage unavailable

Supplementary Table S2. Online tools to examine functional motifs in 3'UTRs

MBS	<p>ALGORITHMS TO PREDICT MBSs IN ANNOTATED 3'UTRs</p> <p>Prone to false positive/negative predictions. Combination of different algorithms can increase the accuracy.</p> <p>Targetscan (http://www.targetscan.org/vert_71/)</p> <p>PITA (https://genie.weizmann.ac.il/pubs/mir07/mir07_data.html)</p> <p>DIANA-microT4 (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=microtv4/index)</p> <p>mirMap (http://mirmap.ezlab.org/)</p> <p>RNA22 (https://cm.jefferson.edu/rna22/Interactive/)</p> <p>miRANDA (http://www.microrna.org/microrna/home.do)</p> <p>microRNAmap (http://mirnamap.mbc.nctu.edu.tw/)</p> <p>RNAhybrid (https://bibiserv2.cebitec.unibielefeld.de/rnahybrid?id=rnahybrid_view_submission)</p> <p>MiRBridge (http://mirsystem.cgm.ntu.edu.tw/)</p> <p>PICTAR (http://pictar.mdc-berlin.de/)</p> <p>miRtarget (Access via miRWalk), microTar (http://tiger.dbs.nus.edu.sg/microtar/)</p>
	<p>ONLINE DATABASES OF PREDICTED MBSs IN ANNOTATED 3'UTRs</p> <p>Allows the combination of different algorithms in the prediction. Curated so may not always include the latest versions of the algorithms.</p> <p>miRDB (http://www.mirdb.org/miRDB/)</p> <p>miRWalk (http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/)</p> <p>miRGate (http://mirgate.bioinfo.cnio.es/miRGate/)</p> <p>miRANDA (http://www.microrna.org/microrna/home.do)</p>
	<p>ALGORITHMS THAT COMBINE EMPIRICAL AND THEORETICAL MBS DATA</p> <p>The interaction between mRNA and miRNA can vary between tissue and cell types and might be affected by experimental setup.</p> <p>TarPmiR (http://hulab.ucf.edu/research/projects/miRNA/TarPmiR/)</p> <p>MEME-DREME (http://meme-suite.org/index.html)</p>
	<p>ONLINE DATABASES OF EXPERIMENTALLY VALIDATED mRNA-miRNA INTERACTIONS</p> <p>The interaction between mRNA and miRNA can vary between tissue and cell types and might be affected by experimental setup</p> <p>miRDB (http://www.mirdb.org/miRDB/)</p> <p>miRGate (http://mirgate.bioinfo.cnio.es/miRGate/)</p> <p>miRANDA (http://www.microrna.org/microrna/home.do)</p>

	<p><u>ONLINE DATABASES PREDICTING EFFECTS OF MBS VARIANTS</u> Requires established SNPs with rs-numbers as input. Therefore rare mutations or rare variants may not be applicable. miRSNP (http://bioinfo.bjmu.edu.cn/mirsnp/search/) miRVaS (http://mirvas.bioinf.be/index.html) STARmiR (http://sfold.wadsworth.org/cgi-bin/starmir.pl)</p> <p><u>ONLINE DATABASES OF DISEASE ASSOCIATED SNPs IN OR NEAR MBSs</u> Requires established SNPs with rs-numbers as input. Therefore rare mutations or rare variants may not be applicable. miRSNP (http://bioinfo.bjmu.edu.cn/mirsnp/search/) miRdSNP (http://mirdsnp.ccr.buffalo.edu/)</p> <p><u>ONLINE DATABASES OF miRNA EXPRESSION PATTERNS</u> Show the expression of miRNAs at a given time in different tissues. The miRNA expression pattern might differ during development. miRANDA (http://www.microrna.org/microrna/home.do) miRGator (http://mirgator.kobic.re.kr/) miRWalk (http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/)</p>
RBP	<p><u>ALGORITHMS TO PREDICT RBP BINDING SITES</u> RBP binding sites are often very short motifs and depend on the secondary structure of the RNA. As such, they are difficult to predict based on sequence alone. Empirical data can be included to increase the accuracy but there may be biases based on cell type or experimental setup. RBPMAP (http://rbpmap.technion.ac.il/) RBPDB (http://rbpdb.ccb.utoronto.ca/) driMUST (http://drimust.technion.ac.il/index.html) MEMERIS (http://www.bioinf.uni-freiburg.de/~hiller/MEMERIS/) CIS-BP-RNA (http://cisbp-rna.ccb.utoronto.ca/index.php) RBPmotif (http://www.rnamotif.org/) catRAPID (http://s.tartagliolab.com/page/catrapid_omics_group) ATtRACT (https://attract.cnic.es/) rMAPS (http://rmaps.cecsresearch.org) POSTAR (http://lulab.life.tsinghua.edu.cn/postar/)</p>

	<p><u>ONLINE DATABASES OF EXPERIMENTALLY VALIDATED mRNA-RBP INTERACTIONS</u></p> <p>The interaction between mRNA and RBP can vary between tissue and cell types and might be affected by experimental setup</p> <p>RBPDB (http://rbpdb.cabr.utoronto.ca/)</p> <p>doRiNA (http://dorina.mdc-berlin.de/)</p> <p>CIS-BP-RNA (http://cisbp-rna.cabr.utoronto.ca/index.php)</p> <p>RBP-Var (http://www.rbp-var.biols.ac.cn/)</p> <p>RAID (http://www.rna-society.org/raid/)</p> <p>CLIPdb (http://lulab.life.tsinghua.edu.cn/clipdb/)</p> <p>POSTAR (http://lulab.life.tsinghua.edu.cn/postar/)</p>
	<p><u>CURATED DATABASES OF RNA BINDING PROTEINS</u></p> <p>As a curated database, it is very reliable but might not always be completely up to date.</p> <p>READDB (http://darwin.soic.iupui.edu/)</p>
PolyA	<p><u>ALGORITHMS TO PREDICT POLY-A SITES FROM USER PROVIDED SEQUENCES</u></p> <p>Accurate for the prediction of different polyA sites, but should be complemented with experimental evidence to confirm the presence of different 3'UTRs.</p> <p>polyApred (http://www.imtech.res.in/raghava/polyapred/)</p> <p>poly(A) Signal (http://dnafsmineer.bic.nus.edu.sg/PolyA.html)</p> <p>Dragon PolyA Spotter (DPS) (http://www.cbrc.kaust.edu.sa/dps/)</p>
	<p><u>ONLINE DATABASES OF EXPERIMENTALLY DETERMINED POLY-A AND APA EVENTS</u></p> <p>As curated databases, they are very reliable but might not always be completely up to date.</p> <p>APADB (http://tools.genxpro.net/apadb/)</p> <p>PACDB (http://harlequin.jax.org/pacdb/)</p> <p>PolyAsite (http://polyasite.unibas.ch/)</p>
3'UTRs	<p><u>CURATED DATABASE OF MULTIPLE MOTIF TYPES IN UTR SEQUENCES</u></p> <p>As a curated database, it is very reliable but might not always be completely up to date.</p> <p>UTRdb (http://utrdb.ba.itb.cnr.it/)</p> <p>AURA (http://aura.science.unitn.it/)</p>

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