SUPPLEMENTARY DATA

RNA G-quadruplexes: emerging mechanisms in disease

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Supplementary Table 1. **Functional RNA G4s and the associated mechanisms in health and disease.**

RNA G-QUADRUPLEXES								
Gene Code (HGNC)	**Gene description**	**Gene-disease association**	**Position**	**Function**	**Methods**	**RBP**	**G4-associated biological process**	**Ref.**
NRAS	Neuroblastoma RAS Viral (V-Ras) Oncogene Homolog	Cancer	5' UTR	Translation repressor	-Reporter (*in vitro*) -UV, CD	N.D.	N.D	(1,2)
ESR1	Estrogen Nuclear Receptor Alpha	Breast Cancer, Osteoporosis, Alzheimer	5' UTR	Translation repressor	-Reporter (*in vitro*) -UV, CD	N.D.	N.D.	(3)
			ORF		-Reporter (*in vitro/in cellulo)* -UV, CD, native PAGE	N.D.		(4)
ZIC1	Zic family member 1	Medulloblastoma	5' UTR	Translation repressor	-Reporter *(in cellulo)* -UV, CD	N.D.	N.D.	(5)
BCL2	B-cell CLL/lymphoma 2	Cancer, B-cell lymphomas, Alzheimer, Parkinson	5' UTR	Translation repressor	-Reporter (*in vitro/in cellulo)* -UV, CD	N.D.	N.D.	(6)
TERF2	Telomeric repeat binding factor 2	Werner syndrome	5' UTR	Translation repressor	-Reporter (*in vitro/in cellulo)* -UV and CD, native PAGE -G4 ligand 360A, Phen-DC3, Phen-DC6	N.D.	N.D.	(7)
MT3-MMP	Matrix metallopeptidase 16	Gastric, Prostate cancer, Osteochondrosis	5' UTR	Translation repressor	-Reporter *(in cellulo)* -CD, RNAse T1 footprinting -G4 ligand TMPyP4	N.D.	N.D.	(8,9)
ADAM10	ADAM metallopeptidase domain 10	Alzheimer, Cancer	5' UTR	Translation repressor	-Reporter (*in vitro/in cellulo)* -CD	N.D.	N.D.	(10)
				Translation repressor	-Reporter (*in cellulo)* -CD	eIF4A	T-cell acute lymphoblastic leukemia development	(11)
CCND3	Cyclin D3	Cancer , B-cell lymphomas	5' UTR	Translation repressor	-Reporter *(in cellulo)* -CD, RNAse T1 footprinting	N.D.	Cell cycle distribution and proliferation	(12)
AKTIP	AKT interacting protein	Tenosynovitis thymic hyperplasia	5' UTR	Translation repressor	-Reporter (*in vitro)* -UV, CD	N.D.	N.D.	(13)
CTSB	Cathepsin B	Alzheimer, Cancer					N.D.	
FOXE3	Forkhead box E3	Congenital aphakia	5' UTR	Translation activator	-Reporter (*in vitro)* -UV, CD	N.D.	N.D.	(13)

PIM1	Pim-1 proto-oncogene, serine/threonine kinase	Alpha 1-antitrypsin deficiency, Cancer	3' UTR	Translation repressor	-Reporter (*in cellulo)* -UV, CD	N.D.	N.D.	(14)
FGF2	Fibroblast growth factor 2	Cancer, Vascular disease	5' UTR (IRES)	Translation activator	-Reporter *(in cellulo)* -Enzymatic and chemical probing, primer extension	N.D.	N.D.	(15)
VEGFA	Vascular endothelial growth factor A	Cancer, Diabetic retinopathy	5' UTR (IRES)	Translation activator	-Reporter *(in vitro/in cellulo)* -CD, RNAse T1, DMS footprinting	N.D.	N.D.	(16)
				Translation repressor	-Reporter *(in vitro/in cellulo)* -VEGF expression, polysomal analysis of endogenous mRNA -Primer extension -G4 ligand 360A, Phen-DC3, Phen-DC6	N.D.	Endogenous VEGF secretion	(17)
TGFB2	Transforming growth factor beta 2	Cancer, Kidney/lung disease	5' UTR	Translation activator	-Reporter *(in cellulo)* -CD, RNAse T1 footprinting -G4 ligand TMPyP4	N.D.	N.D.	(18)
PP2Ac	Protein phosphatase 2A catalytic subunit	Cancer, Alzheimer	5' UTR	Translation repressor	-Primer extension -EMSA	FMRP	FMRP controls actin cytoskeleton remodeling through regulation of PP2Ac expression	(19)
FMR1	Fragile X mental retardation 1	FXS, FXTAS, Premature ovarian failure, Autistic disorder	5' UTR	Translation repressor	-Reporter (*in vitro/in cellulo)* -RNAse T1 , Native PAGE	hnRNP A2 CBF-A	hnRNP A2 and CBF-A enhance the *in vivo* translation of fragile X premutation mRNA	(20)
			ORF	Translation repressor	-Reporter harbouring the G4 in the 5'UTR (*in vitro)* -Primer extension, DMS footprinting	FMRP	N.D.	(21)
				Alternative splicing	-Reporter and endogenous mRNA expression (*in cellulo/in vivo)* -Primer extension	FMRP	FMRP controls its own splicing at exon 15	(22)
PSD-95 (DLG4)	Discs large homolog 4	FXS, Alzheimer, Schizophrenia	3' UTR	mRNA localization	-Reporter (*in cellulo)* -Enzymatic and chemical probing, primer extension	FMRP	FMRP-mediated neurite mRNA targeting	(23)
				Access of miR-125a to the PSD-95 mRNA	-UV,CD, fluorescence, NMR, native PAGE	Translational regulation of PSD-95 by FMRP and miR-125a (24)		(25)
NR2B	N-methyl-D-aspartate (NMDA) Receptor subunit B	FXS, Schizophrenia , Alzheimer	3' UTR	Translation repressor (26)	-UV,CD, fluorescence, NMR, native PAGE -EMSA	FMRP	FMRP-mediated control of "local" mRNA translation in neurons (27)	(28)
SHANK1	SH3 and multiple ankyrin repeat domains proteins	FXS, Autistic disorder	3' UTR	Translation repressor (26)	-UV,CD, fluorescence, NMR spectroscopy, native PAGE -RNA-pull down	FMRP	FMRP-mediated control of "local" mRNA translation in neurons (27)	(29)
MAP1B	Microtubule associated protein 1B	FXS, Werdnig-Hoffmann disease	5' UTR	Translation repressor (26)	-UV,CD, fluorescence, NMR, native PAGE -EMSA	FMRP	Microtubule stability in brain neuron development (30,31).	(32)

SEMA3F	Semaphorin 3F	FXS	3' UTR	Translation repressor (26)	-UV,CD, fluorescence, NMR, native PAGE	FMRP	FMRP-mediated control of "local" mRNA translation in neurons (27)	(33)
APP	Amyloid beta precursor protein	Cancer, Alzheimer, FXS	ORF	Translation repressor	-RIP-RNAseT1, CLIP	FMRP	FMRP-mediated control of "local" mRNA translation in neurons (27)	(34)
YY1	YY1 transcription factor	Cancer	5' UTR	Translation repressor	-Reporter (*in cellulo)* -CD, DMS footprinting	N.D.	N.D.	(35)
PITX1	Paired like homeodomain 1	Club foot	3' UTR	Translation	-Reporter (*in cellulo)* -Native PAGE -RNA-pull down, EMSA	RHAU	N.D.	(36)
MST1R	Macrophage stimulating 1 receptor	Cancer	5' UTR	Translation repressor	-Reporter (*in vitro/in cellulo)* -Primer extension -G4 ligand Phen-DC3, Phen-DC6	hnRNP A1	-Cell invasion, migration -Breast cancer	(37)
MLL1 MLL4	Mixed-Lineage Leukemia 1, Mixed-Lineage Leukemia 4	Leukemia	ORF	Translation repressor	-Reporter *(in cellulo)* -Polysome analysis -RNA-pull down, CLIP -In-line probing	Aven RHAU	Survival of leukemic cells	(38)
NkX2-5	NK2 homeobox 5	Congenital heart disease	5' UTR	Translation repressor	-Reporter *(in cellulo)* -RNA-pull down, IP	RHAU	Post-transcriptional regulation of Nkx2-5 during heart development	(39)
C9orf72 r(GGGGCC)n RNA	Chromosome 9 open reading frame 72	ALS, FTD	Intron 1	RBP sequestration	-G4 ligand: TMPyP4 -UV,CD, native PAGE -EMSA	hnRNP A1 ASF/SF2	Role of RBPs in toxic RNA pathways	(40)
				RBP sequestration	-Native PAGE, CD -EMSA	ASF/SF2	G4-mediated RNA-RNA interactions influence the formation of toxic RNA foci	(41)
				RBP sequestration	-Native PAGE, CD, RNAse T1 -RNA-pull down	Nucleolin	-Defective nucleolar function and perturbation in protein homeostasis	(42)
				RBP sequestration	-RNA foci: FISH, IF -RNA-pull down	hnRNP H	Neuronal apoptotic cell death	(43)
				RBP sequestration	-RNA foci: FISH, IF -RNA-pull down	ASF/SF2 hnRNP H/F ALYREF hnRNP A1	Toxic RNA foci formation possibly impacting RNA homeostasis through RBP sequestration	(44)
				mRNA transport	-RNA-pull down -Effect of TMPyP4 on nuclear import defects and on neurodegeneration	RanGAP	-Nuclear pore complex defects -Developmental defects	(45)
				Translation Repression (46)	-Fluorescence, native PAGE -RNA-pull down -IF (SG formation) -Reporter *(in vitro)* -G-rich oligo transfection	YB1	Cytoprotective and prosurvival functions (46)	(47)
BCL2, others	B-cell CLL/lymphoma 2	Cancer, B-cell lymphomas, Alzheimer, Parkison	5' UTR	Translation repressor	-Reporter *(in cellulo)* -CD	eIF4A	T-cell acute lymphoblastic Leukemia development	(11)
IGF2	Insulin-like growth factor II	Beckwith-Wiedemann, Proteus syndrome,	3' UTR	Pre-mRNA 3' end processing	-Enzymatic and chemical probing, primer extension, native PAGE	N.D.	Post-transcriptional gene expression regulation by endonucleolytlc	(48)

		Cancer					cleavage	
TP53	Tumor protein TP53	Cancer, Li-Fraumeni syndrome	Pre-mRNA 3' end	Pre-mRNA 3' end processing	-Reporter (*in cellulo*) -Primer extension -G4 ligand TMPyP4 -RNA-pull down, UV crosslinking	hnRNP H/F	TP53 functions, including apoptosis	(49)
			Intron 3	Alternative splicing	-UV,CD, primer extension -Reporter *(in cellulo)* -G4 ligand 360A on endogenous mRNA	N.D.	Production of TP53 isoforms	(50)
CSB II	Conserved Sequence Block II (at mitochondrial DNA)	-	CSBII	Transcription termination	-Reporter (*in vitro*) -Effect of 7-deaza-GTP and ionic conditions on transcription termination -Native PAGE	N.D.	Generation of primers for initiation of mitochondrial DNA replication	(51)
LRP5	Low density lipoprotein receptor-related protein 5	Osteoporosis-pseudoglioma syndrome	3' UTR	Alternative pre-mRNA 3’ end processing	-Reporter *(in cellulo /in vitro)* -CD, In-line probing	N.D	Regulation of mRNA 3’ end length	(52)
FXR1	Fragile X-related mental retardation autosomal homolog 1	FXS						
CaMK2a	Calcium/calmodulin dependent protein kinase II alpha	Cancer	3' UTR	mRNA localization	-Reporter (*in cellulo)* -Enzymatic, chemical probing, primer extension	FMRP	FMRP-mediated neurite mRNA targeting	(23)
BACE1	Beta-site APP (Aβ precursor protein) cleaving enzyme 1	Alzheimer	Exon3	Pre-mRNA Splicing	- Reporter and endogenous mRNA expression (*in cellulo*) -RNAse T1 assay, NMR, CD -EMSA, RNA-pull down	hnRNP H	BACE1 splicing regulates amyloid b-protein involved in the pathogenesis of Alzheimer disease	(53)
PAX9	Pax homeodomain family of transcription factor	Tooth agenesis	Intron 1	Pre-mRNA Splicing	-Reporter and endogenous expression (*in cellulo*) -CD, FRET -G4-ligand 360A	N.D.	Splicing mechanism that might contribute to the modulation of dentition pattern in placental mammals	(54)
Mir-92b	miRNA 92b	Cancer	Pre-miR	MicroRNA maturation	-RNAse T1, native EMSA, CD, chemical and enzymatic mapping -Reporter (*in vitro/in cellulo)*	N.D.	Gene expression regulation through miRNA biogenesis modulation	(55)
Immunoglobulin switch RNA	-	-	N.D.	DNA recombination	-CD, native EMSA -RNA-pull down	AID	Class-switch recombination	(56)
EBAG9	Estrogen Receptor Binding Site Associated, Antigen, 9	Cancer	5' UTR	Translation repressor	-Reporter (*in cellulo*) -CD -In-line probing	N.D.	-	(57)
FZD2	Frizzled Class Receptor 2	Omodysplasia						
BARHL1	BarH-Like Homeobox 1	Joubert syndrome						
NCAM2	Neural cell adhesion molecule 1	-						
THRA	Thyroid hormone receptor alpha	Hypothyroidism						

AASDHPPT	Aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	-						
piRNA precursor	Piwi-interacting RNA	-	3'UTR	piRNA precursor intermediate fragment production	- CLIP, RIP using BG4 -Endogenous level of piRNA precursor	MOV10L1	piRNA biogenesis	(58)
Hsa-miR-3620-5p	Human miRNA 3620-5p	-	-	Access of miR-3620-5p to the its mRNA target	-ESI-MS, CD, NMR, SPR	N.D.	miRNA target recognition	(59)
EBNA1	Epstein-Barr virus encoded nuclear antigen 1	Burkitt's lymphoma, Nasopharyngeal carcinoma, Hodgkin's lymphoma	ORF	Translation repressor	-CD and UV -*In vitro* translation, metabolic labelling, polysome analysis - G4 ligand: antisense oligos, PDS	N.D.	Translation inhibition of virally encoded maintenance proteins, affecting antigen presentation (60)	(61)
hTR/TERC	Telomerase RNA component	Dyskeratosis congenita	5' end	G4-duplex competition (62)	-Native PAGE -RNA-pull down, EMSA	RHAU	Template boundary definition in human telomerase	(63)
hTERT	Human telomerase reverse transcriptase	Cancer	Intron 6	Pre-mRNA Splicing	-Endogenous mRNA expression (*in cellulo*) -G4 ligand 12459	N.D.	hTERT splicing controlling telomerase expression	(64)
TERRA	Telomeric containing RNA	Cancer	-	-	-EMSA -CD	EWS	Putative role in telomere homeostasis	(65,66)
			-	Histone modification of telomeres and telomere length	-	TLS/FUS	Telomere homeostasis	(67)
			-	TERRA association to telomeric DNA	-CD, UV spectroscopy	TRF2	Telomere organization	(68)
			-	Repression of innate immune gene expression	-mRNA expression (*in cellulo*/*in vivo*)	N.D.	Counteracts cancer malignancy	(69)

ALS, amyotrophic lateral sclerosis; CD, circular dichroism; CLIP, crosslink immunoprecipitation; DMS, dimethyl sulfate; EMSA, electrophoretic mobility shift assay; ESI-MS, electrospray ionization-mass spectrometry; ESR, surface plasmon resonance; FISH, florescence *in situ* hybridization; FRET, fluorescence resonance energy transfer; FTD, frontotemporal degeneration; FXS, fragile X syndrome; FXTAS, fragile X-associated tremor/ataxia syndrome; IF, immunofluorescence; NMR, nuclear magnetic resonance; PAGE, polyacrylamide gel electrophoresis; RIP, RNA immunoprecipitation; UV, ultraviolet; N.D, non determined.

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