SnapShot: FMRP mRNA Targets and Diseases

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Gene Name	Protein Name	Molecular Function	UniProt Entry	OMIM ID	Disease
MAP1B	Microtubule-associated protein 1B	Microtubule-associated protein	P46821	157129	Alzheimer's disease, Huntington's disease, cancer
CAMK2A	Calcium/calmodulin-dependent protein kinase type II alpha chain	Protein kinase	Q9UQM7	114078	Bipolar disorder, schizophrenia, Alzheimer's disease, depression, Huntington's disease
FMR1	Fragile X mental retardation gene 1	RNA-binding protein	Q06787	309550	Fragile X syndrome, autism, premature ovarian failure, fragile X tremor ataxia, Parkinson's disease, cancer, immune disease, schizophrenia, bipolar disorder, major depressive disorder
APP	Amyloid precursor protein	Transmembrane protein/cell signalling	P05067	104760	Schizophrenia, cerebral amyloid angiopathy, Alzheimer's disease, Down syndrome, cancer, amyotrophic lateral sclerosis, major depressive disorder, immune disesases, autism
DLG4	Postsynaptic density protein 95 (PSD-95)	Cytoskeleton/scaffolding	P78352	602887	Schizophrenia, autism, cancer, bipolar disorder
ARC	Activity-regulated cytoskeleton-associated protein	Actin-binding protein	Q7LC44	612461	Epilepsy, Alzheimer's disease
GABRD	Gamma-aminobutyric acid receptor subunit delta	Transmembrane protein/receptor	O14764	137163	Schizophrenia, bipolar disorder, major depressive disorder, epilepsy
DLGAP4	SAP90/PSD-95-associated protein 4 (SAPAP4)	Cell membrane	Q9Y2H0	na	Cancer
MBP	Myelin basic protein	Membrane protein	P02686	159430	Schizophrenia, bipolar disorder, Parkinson's disease
AATK	Serine/threonine-protein kinase LMTK1	Kinase	Q6ZMQ8	605276	Cancer
GABRB1	Gamma-aminobutyric acid receptor subunit beta-1	Transmembrane protein/receptor	P18505	137190	Schizophrenia, bipolar disorder, major depressive disorder, autism, cancer
MMP9	Matrix metalloproteinase 9	Enzyme/collagenase/gelatinase	P14780	120361	Amyloidosis, schizophrenia, immune disease, cancer
KCNC1	Voltage-gated potassium channel subunit Kv3.1	Transmembrane protein/ion channel	P48547	176258	Alzheimer's disease, Huntington's disease, immune disease
KCND2	Voltage-gated potassium channel subunit Kv4.2	Transmembrane protein/ion channel	Q9NZV8	605410	Autism, cancer
MAP2	Microtubule-associated protein 2	Microtubule-associated protein	P11137	157130	Autism, cancer, Huntington's disease
PIK3CB	p110beta, phosphatidylinositol 4,5-bisphosphate 3-kinase 110 kDa catalytic subunit beta	Kinase	P42338	602925	Schizophrenia, immune disease
SOD1	Superoxide dismutase 1	Enzyme	P00441	147450	Amyotrophic lateral sclerosis, Parkinson's disease, cancer
RGS5	Regulator of G protein signaling 5	GTPase activator	O15539	603276	Cancer
RAC1	Ras-related C3 botulinum toxin substrate 1	GTP-binding protein	P63000	602048	Cancer
RHOA	Ras homology gene family, member A	GTP-binding protein	P61586	165390	Amyotrophic lateral sclerosis, cancer, immune disease
ARHGEF12	Rho guanine nucleotide exchange factor 12	Cytoplasmic/membrane protein/G protein-coupled receptor binding	Q9NZN5	604763	Cancer
SPEN	Msx2-interacting protein	DNA/RNA binding	Q96T58	613484	Cancer
NR3C1	Glucocorticoid receptor, group C, member 1	Membrane protein/adhesion molecule	P04150	138040	Bipolar disorder, major depressive disorder, schizophrenia
CTNNB1	Catenin β-1	Membrane protein and transcriptional factor	Q02248	116806	Cancer, autism
PCLO	Piccolo	Protein transporter	Q9QYX7	604918	Schizophrenia, cancer
EEF2	Eukaryotic translation elongation factor 2	GTP-binding protein	P58252	130610	Spinocerebellar ataxia, Alzheimer's disease, immune disease
APC	Adenomatous polyposis coli	Microtubule-binding protein/kinase regulator	P25054	175100	Familial adenomatous polyposis, cancer, schizophrenia, bipolar disorder, autism
ALDOA	Fructose-bisphosphate aldolase A	Enzyme/scaffolding	P05064	103850	Glycogen storage disease XII, cancer, immune diseases, schizophrenia
AP2B1	AP-2 complex subunit β-1	Protein transporter	Q9DBG3	601025	Neurodegeneration
FUS	RNA-binding protein FUS	DNA/RNA-binding protein	P35637	137070	Alzheimer's disease, amyotrophic lateral sclerosis, cancer
VDAC1	Voltage-dependent anion-selective channel protein 1	Transmembrane protein/Ion channel	P21796	604492	Schizophrenia, Alzheimer's disease, cancer
HNRNPA2B1	Heterogeneous nuclear RiboNucleoProtein A2/B1	RNA-binding protein	P22626	600124	Inclusion body myopathy, Alzheimer's disease, immune disease
PKP4	Plakophilin 4	Adhesion molecule	Q99569	604276	Cancer
NLGN2	Neuroligin 2	Transmembrane protein/receptor	Q8NFZ4	606479	Autism, cancer
DAG1	Dystrophin-associated glycoprotein 1	Enzyme	Q14118	613818	Cancer, muscular dystrophy-dystroglycanopathy type C7, immune system
PCDH10	Protocadherin 10	Membrane protein/adhesion molecule	Q9P2E7	608286	Autism, cancer, schizophrenia
PLP1	Myelin proteolipid protein	Membrane protein	P60201	300401	Pelizaeus-Merzbacher disease, spastic paraplegia, schizophrenia, cancer
PTPN5	Striatum-enriched protein tyrosine phosphatase (STEP)	Phosphatase	P54829	176879	Huntington's disease
OPHN1	Oligophrenin 1	Membrane protein/adhesion molecule	O60890	300127	X-linked mental retardation, autism spectrum disorders, schizophrenia
PPP2CA	Catalytic subunit of protein phosphatase 2	Phosphatase	P67775	176915	Immune disease, Down syndrome

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The fragile X syndrome (FXS) is an X-linked condition and the leading monogenic cause of intellectual disability and autism (Bagni et al., 2012); it was first described by Martin and Bell in 1943. Patients with FXS show several neurological symptoms, including intellectual disability, hyperactivity, obsessive-compulsive disorders, anxiety, and autistic-like behavior (Jacquemont et al., 2007). The causative gene *FMR1* was identified in 1991 as a joint and concomitant effort by the laboratories of Stephen T. Warren, Ben A. Oostra, Jean-Louis Mandel, Grant R. Sutherland, and David L. Nelson.

FMRP, the protein encoded by the *FMR1* gene, is either absent or mutated in FXS patients (Bagni et al., 2012; Jacquemont et al., 2007). FMRP binds to mRNA and regulates translation (Bagni et al., 2012) as well as transport and stability of its targets (Bassell and Warren, 2008; De Rubeis and Bagni, 2010). Presumably, dysregulation of the mRNA targets causes the FXS phenotypes, and it is therefore important to understand which mRNAs are controlled by FMRP.

Several high-throughput approaches such as coimmunoprecipitation followed by microarray analysis (Brown et al., 2001), CLIP-RNA sequencing (Darnell et al., 2011, Ascano et al., 2012), and antibody-positioned-RNA amplification (APRA) (Miyashiro et al., 2003) led to the identification of hundreds of FMRP putative target mRNAs (>1,000 in brain and >6,000 in nonneuronal cells). Overall, FMRP was shown to bind almost 4% of the mouse brain transcriptome (Brown et al., 2001; Miyashiro et al., 2003; Darnell et al., 2011). The effect of FMRP binding to the majority of these target mRNAs still needs to be elucidated. Here, we report on 40 bona fide FMRP targets for which mRNA binding and protein regulation have been reported in mammals by more than one study. The list is sorted by the number of studies reporting on the FMRP/mRNA functional interaction, ranked from orange (most frequent) to white (less frequent). Due to space constraints we needed to limit the list of targets; we apologize to our colleagues whose studies could not be included.

For each gene, the disease associated with the encoded protein is shown; diseases were compiled from the following databases: SFARIgene (https://gene.sfari.org), AutDB (http://autism.mindspec.org), SzGene (http://www.szgene.org), AlzGene (http://www.alzgene.org), PDGene (http://www.pdgene.org), Cosmic (http://cancer.sanger.ac.uk), Ingenuity Pathway Analysis (http://www.ingenuity.com), and GWAS studies.

As expected, many of the FMRP target mRNAs are linked to neurological disorders that can be correlated to aspects of the FXS phenotype, such as autism, schizophrenia, or major depressive disorder. The genes encode for proteins mostly involved in synaptic activity, cell adhesion, and cytoskeleton structure and remodeling, suggesting that dysregulation of these processes is responsible for the neurological phenotypes of FXS.

More than 20 years after its discovery, FMRP continues to reveal new and unexpected clinical presentations and molecular mechanisms. Some FMRP targets are linked to nonneurological disorders, raising the possibility that the FMRP also plays a role in other diseases. Indeed, FMRP is expressed in all tissues, although at lower levels than the brain. An involvement of FMRP in cancer has been shown: the protein is overexpressed in breast cancer (Lucá et al., 2013), and patients with FXS show a decrease in cancer incidence (Lucá et al., 2013; Schultz-Pedersen et al., 2001).

Importantly, not one single gene regulated by FMRP can explain any given disease phenotype. Instead, the pathology appears to arise from the concerted dysregulation of a set of mRNAs, consituting the FMRP regulon, which, under physiologic conditions and at different developmental stages, is orchestrated by FMRP and its various protein interactors.

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