Disruption of RNA metabolism in Neurological Disorders

A number of genes that play important roles in RNA metabolism have been implicated in neurological disorders. These are summarized in the table below. The 3' UTR CTG/CCTG expansions that occur in myotonic dystrophy cause mRNA to accumulate in foci which then sequester factors important for the correct adult splicing pattern of various genes such as the *Muscle Chloride Channel.*[1,2] Dominant Retinitis Pigmentosa (RP) can be caused by mutations in the ubiquitously expressed proteins (PRPF31, PRPF8 and HPRP3) that are essential for the correct assembly and function of the U4,U5 andU6 tri-snRNP in pre-mRNA splicing.[2,3] In retinal cell cultures mutant PRPF31 alters the efficiency of intron 3 removal from rhodopsin pre-mRNA, reducing rhodopsin and resulting in cell death.[4] In Prader-Willi syndrome loss of HB11-52, a small nucleolar RNA (snoRNA), alters the alternative splicing of the *Serotonin 2C Receptor*.[2,5] Recently mutations in *TAR DNA-binding protein 43* (*TDP-43*) and *fused in sarcoma/translated in liposarcoma* (*FUS/TLS*), RNA binding proteins important for splicing of certain genes,[6-9] have been reported to cause ALS.[10-13] There is therefore a precedent for mutations in essential genes involved in pre-mRNA splicing resulting in degeneration of specific groups of neurons. There can often also be unexpected links between the genes mutated in a particular disease and RNA metabolism. The gene mutated in X-linked SMA has been identified as *ubiquitin activating enzyme (UBE1).*[14] Thus it might appear that this disease results from the disruption of a separate cellular pathway from the SMN and splicing pathway that causes proximal SMA. However altering ubiquitination reduces the level of U4/U6-U5 snRNP,[15] a critical component of the spliceosome, and thus splicing could be altered in this disorder.

As can be seen in the table below, not all mutations in RNA metabolism act through splicing. *Senataxin* mutations give rise to motor neuron disease or ataxia[16] and mutations in *immunoglobulin μ binding protein 2 (IGHMBP2)* give rise to distal SMA.[17] Both proteins contain a similar RNA helicase domain and both are involved in tRNA and rRNA biogensis.[18,19] Mutations in *glycyl-t-RNA synthetase* and *tyrosyl-t-RNA synthetase* cause the peripheral neuropathy CMT.[20,21] In mice loss of function alleles for these two genes does not mimic the peripheral neuropathy rather missense mutation that disrupt a particular property of tRNA-synthetase cause CMT. Interestingly the products of these mutant alleles are unable to localize to the distal axon in the same way that the wild-type protein does.[22,23] It is possible that this causes a deficiency of the enzyme at that site and, thus, CMT. In SMA it seems possible that either an alteration in the splicing of certain genes or in the localization of mRNA could be critical to the development of the phenotype. An understanding of how reduced SMN causes SMA may have a wider impact on our understanding of how mutations in genes important for RNA metabolism cause neurogenetic disease.

Supplementary table 1 RNA metabolism and neurological disease

Disease	Molecular Defect	Consequence	Ref
DM1, DM2	CUG/CCUG expansion in 3' UTR RNA binds splicing factors	Altered Splicing	1,2
FXS	CGG expansion in 5'UTR reduced FRAX expression	Altered Translation	24
SCA8	CUG expansion in 3'UTR	? Altered splicing	25
HDL2	CTG expansion in alternate RNA binds splicing factors	? Altered splicing	26
OPMD	GCG expansion in *PAPBN1*	Polyadenylation	27

POMA	Autoantibodies to *Nova 1*	Altered splicing	[28]
Hu syn	Autoantibodies to Hu proteins	mRNA stability, export	[29]
MRS	Mutations in *UPF3B*	Nonsense mediated decay	[30]
PWS	Loss of *SNURF* expression	Altered splicing (Serotonin receptor)	[5]
RP	Mutations in *PRPF31,8,3*	? Altered splicing Rodopsin	[3,4]
LAAHD/ LCCS	Mutations in *GLE1*	Altered transport of mRNA from nucleus	[31]
ALS	Mutations in *SOD1*	? unknown	[32]
ALS	Mutations in *TDP43*	? altered splicing	[8,10,11]
ALS	Mutations in FUS/TLS	? altered splicing	[12,13]
DSMA	Mutations in *IGHMBP2*	?altered translation	[17,18]
CMT	*tRNA synthetase*	? Axon problem	[20-23]
SMA	Loss of *SMN1,* retention *SMN2*	? altered splicing/RNA transport	[33]

Abbrevations: Diseases: DM Myotonic muscular dystrophy, FXS Fragile X syndrome, SCA spinocerebellar ataxia, HDL Huntington disease like, OMPD oculopharyngeal muscular dystrophy, POMA opsoclonus-myoclonus ataxia, Hu syn Hu syndrome, MRS Mental retardation syndrome, PWS Prader-Willi syndrome, RP Retinitis pigmentosa, LAAHD Lethal arthrogryposis with anterior horn cell disease, LCCS Lethal congenital contracture syndrome, ALS Amyotrophic Lateral Sclerosis, DSMA distal spinal muscular atrophy, CMT Charcot-Marie-Tooth Disease, SMA spinal muscular atrophy, Genes: FRAX fragile X protein, PAPBN1 Poly(A) binding protein nuclear 1, Nova 1 neuro-oncological ventral antigen 1, UPF3B regulator of nonsense transcripts homolog B, SNURF SNRPN upstream reading frame–small nuclear ribonucleoprotein polypeptide N, PRPF 31or 8 or 3 pre-mRNA processing factor 31 or 8 or 3, GLE1 GLE1 mRNA export mediator homolog, SOD1 Superoxide dismutase 1, TDP43 TAR DNA binding protein 43, FUS/TLS fused in sarcoma/translated in liposarcoma, IGHMBP2 immunoglobulin mu binding protein 2, SMN survival motor neuron. Table adapted from Lukong et al.[34]

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