Evolutionary Conservation and Expression of Human RNA-Binding Proteins and Their Role in Human Genetic Disease

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Abstract

RNA-binding proteins (RBPs) are effectors and regulators of posttranscriptional gene regulation (PTGR). RBPs regulate stability, maturation, and turnover of all RNAs, often binding thousands of targets at many sites. The importance of RBPs is underscored by their dysregulation or mutations causing a variety of developmental and neurological diseases. This chapter globally discusses human RBPs and provides a brief introduction to their identification and RNA targets. We review RBPs based on common structural RNA-binding domains, study their evolutionary conservation and expression, and summarize disease associations of different RBP classes.

Keywords

1 Principles of Posttranscriptional Gene Regulation

RNA is an essential constituent of all living organisms and central to decoding the genetic information of every cell. Recent advances in RNA sequencing technologies have facilitated the discovery of novel transcripts and we will soon know the precise composition of most cellular transcriptomes. While functional annotation for many RNAs is still in progress, the major classes of RNAs have now been described (Table 1.1). The most abundant RNAs, constituting 90 % of cellular RNAs by copy number, are shared by all organisms and required for protein synthesis: rRNAs, tRNAs, and mRNAs (Table 1.1). The remaining 10 % are noncod-ing RNAs (ncRNAs) that mainly serve as guides or molecular scaffolds in a variety of processes including RNA splicing, RNA modification, and RNA silencing. The structure, length, and composition of these RNAs and their ribonucleoprotein particles (RNP) are distinct and allow their integration into diverse functions and layers of regulation to control target RNAs and their many functions.

Posttranscriptional gene regulation (PTGR) is a term that refers to the cellular processes that control gene expression at the level of RNA; it encompasses RNA maturation, modification, transport, and degradation. Consequently, every RNA molecule independent of its ultimate function is at some level subject to PTGR. RNA- binding proteins (RBPs) are central players

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of PTGR, as they directly bind to RNAs to form RNPs. In many cases, the RNP is the most basic unit, comprising a complex of obligate RNA and protein partners (e.g., snRNPs, snoRNPs, RNase P, ribosome subunits), which elicits its respective function. However, many other types of RNAs, particularly mRNAs and tRNAs, only transiently associate with RBPs, whose functions are necessary for their proper maturation, localization, and turnover (Dreyfuss et al. 2002; Granneman and Baserga 2004; Phizicky and Hopper 2010; Müller-McNicoll and Neugebauer 2013). Indeed most mRNA-binding proteins (mRBPs) have thousands of targets they regulate (Ascano et al. 2011). Hence the proper assembly and function of RNA-protein complexes are critical for development and maintenance of all cells and organisms. For a large fraction of RBPs, we are only starting to understand the complexity of their basic molecular roles, modes of recognition, and global targets.

In this chapter we review the current state of knowledge of the protein components involved in PTGR in humans. We discuss common patterns found among RBPs, based on targets, evolutionary conservation, shared structural domains, and cell-type-specific or ubiquitous expression. We then examine various classes of RBPs commonly implicated in human disease.

2 Human RBPs

2.1 Experimental and Bioinformatic Approaches Leading Towards a Census of RBPs

A complete catalogue of the proteins involved in PTGR is an important goal. Historically, different strategies have been employed towards the identification of RBPs (Ascano et al. 2013). Common approaches used RNA pull-down assays to recover associated proteins in cell lysates, followed by their mass spectrometric identification, or candidate proteins were recombinantly expressed and interrogated for their RNA-binding properties in vitro. These RNA-centric approaches identified the interactome of subsets of RNAs but did not capture the whole RBP proteome, and were not suitably of high throughput.

The first genome-wide approaches for the identification of proteins involved in PTGR utilized predictive methods and searched for the presence of protein domains conferring RNA binding. Early studies on the protein components of heteronuclear RNPs (hnRNPs) led to the identification of the first conserved, canonical RNA- binding domain (RBD) within RBPs (Burd and Dreyfuss 1994). Following these initial discoveries, and facilitated by advances in genome sequencing and the acquisition of protein structures, more precise classification of structural and functional protein domains followed rapidly (Henikoff et al. 1997). Computational prediction algorithms that use probability matrices from multiple sequence alignments enabled the detection of structural domains in uncharacterized protein sequences across organisms. The results of these predictions are publically available in a number of databases such as Interpro, Pfam, SCOP, SMART, or CDD (Murzin et al. 1995; Apweiler et al. 2001; Marchler-Bauer et al. 2003; Letunic et al. 2009; Finn et al. 2010). Among these domain classifications, at least 600 can be found with annotation referring to involvement in RNA-related processes.

Predicting the number of RBPs encoded in various genomes has remained a challenge. RBPs were defined by the presence of one or more canonical RBDs, such as RRM, KH,

CSD, zinc fingers, and PUF domains (Lunde et al. 2007). Selecting these predominantly mRNA-binding RBDs, the number of RBPs was initially estimated to ~400–500 in human and mouse (McKee et al. 2005; Galante et al. 2009; Cook et al. 2011), ~300 in *D. melanogaster* (Lasko 2000; Gamberi et al. 2006), ~250–500 in *C. elegans* (Lasko 2000; Lee and Schedl 2006; Tamburino et al. 2013), and ~500 RBPs in *S. cerevisiae* (Hogan et al. 2008). Inclusion of RNA-processing domains involved in RNA metabolism of every known type of RNA leads to numbers near ~700 RBPs in humans (Anantharaman et al. 2002).

Other predictive approaches such as the Kyoto Encyclopedia of Genes and Genomes database (KEGG) (Kanehisa and Goto 2000) and the Gene Ontology project (GO) (Ashburner et al. 2000) integrate domain annotations, protein homologies, and searches of scientific literature statements. These estimate the number of human proteins with RNA-related functions to ~1,800 proteins (Fig. 1.1). However, these methods are often not reliable due to false classifications of proteins, leading to a large number false positives and false negatives.

In parallel, experimental proteome-wide methods were employed to identify the number of known and novel RBPs such as the development of protein microarrays, which allowed increased throughput for probing the RNA-binding capabilities of a fraction of the proteome in vitro, using RNA probes of defined sequence (Scherrer et al. 2010; Tsvetanova et al. 2010; Siprashvili et al. 2012). In an attempt to comprehensively identify existing and novel RBPs in human at large scale with a singular approach, cross-linking-based methods were recently introduced. In these methods, RBPs were covalently cross-linked to endogenous RNAs using in vivo UV cross-linking, followed by polyA selection of mRNAs, and subsequent identification of interacting proteins by mass spectrometry. These approaches identified ~800 mRBPs in human HEK293 and HeLa cell lines, respectively (Baltz et al. 2012; Castello et al. 2012), 555 in mouse embryonic stem cells (mESCs) (Kwon et al. 2013), and 200 mRBPs in yeast (Mitchell et al. 2013). Together, 1,100 of known and putative human mRBPs were experimentally defined and, assuming homologous function between mouse and human proteins, an additional ~80 proteins may be added (Fig. 1.1a, b). A significant portion of these (64 %) overlapped with known GO-classified RBPs (Fig. 1.1a, b). Many of the residual mRBP candidates did not contain previously described RBDs and require further experimental validation, while other known and expressed RBPs were missed due to the sensitivity of the experiments. However, in comparison to earlier predictive counts of the number of mRBPs (Cook et al. 2011), this approach expanded the mRBP proteome from ~400 to ~1,200 proteins and may, with increasing sensitivity, represent the most suitable method to identify novel RBPs in proteome-wide experiments in different cell types.

Here, we describe our attempt in generation of a curated and comprehensive list of RBPs involved in PTGR processes to guide us in their study of molecular and cellular function and definition of all RNA-related processes.

2.2 Generation of a Curated List of Human RBPs

Our approach selects RBDs involved in RNA-related processes as defined by Pfam (Finn et al. 2010) and searches the human genome for any protein-coding gene that contains at least

one of the selected domains, but remains overall unbiased to the putative function of the gene and its RNA targets. Arriving at a list of 2,130 candidates, we added known RBPs from literature searches with unclassified RBDs and additionally screened proteins defined as RBPs by GO (Ashburner et al. 2000) and proteome-wide mass spectrometry datasets (Baltz et al. 2012; Castello et al. 2012; Kwon et al. 2013) for literature-based evidence of their involvement in PTGR.

The list of RBPs was finalized according to the following main criteria: (1) the proteins possessed defined RNA-binding or RNA-enzymatic domains, (2) the proteins were experimentally shown to be part of RNP complexes and thereby involved in RNA metabolic pathways, or (3) they possessed high sequence identity to homologs and paralogs involved in PTGR. Some of the candidate RBPs identified in the recent cross-linking-mass spectrometry studies were not considered as RBPs, if their RNA-binding activity could not be confirmed independently in other published datasets or their domain structure, family members, and homologs were not indicative of an RBP. We furthermore disregarded proteins containing putative RBDs if they showed strong evidence for exclusive roles in RNA-unrelated pathways, such as the majority of C2H2 zinc finger transcription factors of which only a small subset are RNA-binding, e.g., TF3A binding to 5S rRNA (Brown 2005). We included proteins, which are components of well-defined, large RBP complexes, such as the ribosome or the spliceosome, as it is difficult to establish with certainty which proteins interact with RNA directly or indirectly in these large RNPs. This approach is supported by recent proteome-wide cross-linking studies, and the RNA-binding properties of scaffold proteins CNOT1 and TDRD3 have for example emerged through this process (Thomson and Lasko 2005; Siomi et al. 2010; Baltz et al. 2012; Castello et al. 2012; Kwon et al. 2013). Through this curation process we reduced the union of ~3,700 proteins, derived from domain annotation, mass spectrometry datasets, literature search, and GO annotation, to arrive at a final of 1,542 proteins (Fig. 1.1b). The resulting curated list of RBPs contains proteins interacting with all RNA classes. A comparison to the conventionally named "canonical RBPs" (Lunde et al. 2007; Cook et al. 2011) shows that canonical RBPs only represent one-third of RBPs in this set and the majority of RBPs in our set would not be considered using currently available datasets (Fig. 1.1c). The following sections discuss abundance, evolution, expression, and RBPs in human disease based on this curated set of RBPs.

3 Quantitative Aspects of Proteins in RNA Metabolism

The dynamics of complex assembly and composition of RNPs, their targets, and protein cofactors are extremely sensitive to the quantitative relationship between the abundance of RBPs and their targets (Dreyfuss et al. 2002; Müller-McNicoll and Neugebauer 2013). RBPs are in constant competition for binding to frequently occurring short and degenerated RNA sequence elements and thus the cellular compartment concentration of RNA and RBPs will affect the equilibrium of dynamic RNP formation and disassembly. Processes such as pre-mRNA splicing and alternative polyadenylation, where the choice of alternative splice sites or 3′UTR lengths is dependent on the abundance of splicing enhancers, silencers, or U1 snRNP (Smith and Valcarcel 2000; Kaida et al. 2010; Berg et al. 2012; Kornblihtt et al. 2013), emphasize the importance of determining precise RBP levels.

Approximately 7 % of all protein-coding genes are committed to PTGR, but their contribution to the pool of expressed proteins in cells is much higher. We analyzed expression level of ubiquitous RBPs based on RNA-seq data in HEK293 cells (Teplova et al. 2013) (Fig. 1.2). In this cell line, RBPs represented 9 % (1,364 genes) of the ~16,300 expressed genes (expressed with RPKM > 1), but their corresponding transcripts represent more than 25 % of total cellular mRNA, including 7 % mRBPs and 14 % ribosomal proteins (RBP categorization discussed in next section), stressing the abundance of mRNA metabolism and the central role of protein translation (Fig. 1.2). In contrast, transcription factors and cytoskeletal proteins were not overrepresented in the transcriptome of HEK293 cells. In summary, about a quarter of the transcriptome is committed to RNA metabolism, highlighting its fundamental role in the cell.

4 Paralogous RBP Families and their Targets

Determining the evolutionary relationships and the conservation of gene families has been critical for understanding gene function and emphasized the utility of model organisms for the study of fundamental biological processes (Henikoff et al. 1997). To account for redundancies among RBPs it is therefore beneficial to consider the RBP family as the smallest functional unit. Grouping the 1,542 RBPs into paralogous gene families with at least 20 % homology gives 1,113 RBP families with one or two members on average. The large number of families reflects a high diversity of RBPs in human.

Here, we categorized RBPs and RBP families based on their reported natural targets and examined their distribution and evolutionary relationships among different classes. Although RBPs often show some degree of interaction with a range of target RNAs in vivo, most of them are committed to one subtype of RNA (Hafner et al. 2010; Wang et al. 2012; Ascano et al. 2012; Hussain et al. 2013; Lovci et al. 2013; Wang et al. 2013) (Table 1.1). Some exceptions remain, such as RNA nucleases, and RBPs acting at the interface of two different RNA classes, such as spliceo-somal proteins, XPO5, or EEF1A, recognizing snRNA/ mRNAs, pre-miRNAs/mRNAs, and tRNAs/mRNAs, respectively (Liu et al. 2002; Lund 2004; Mickleburgh et al. 2006; Bennasser et al. 2011; Dever and Green 2012). For the RBPs with multiple targets, we either classified them as diverse in target preference or counted the proteins towards the predominant group of targets based on available literature. The resulting distribution of RBPs and RBP families across all RNA targets in human and their conserved homologs in yeast is shown in Fig. 1.3a–c.

Our analysis shows that mRBPs form the largest group among RBPs comprising 45 % of all human RBPs (~700 proteins). mRBPs frequently represent families of RBPs with more than two members. Ribosomal proteins constitute the next larger group of RBPs with ~170 proteins of the cytosolic and mitochondrial ribosomes. The next smaller groups of RBPs are committed to tRNA (~150) and rRNA (~120) biogenesis pathways, followed by proteins involved in snRNA, snoRNA, and other ncRNA pathways (Fig. 1.3a, b).

Of the ~1,100 human RBP families, ~550 have homologs in yeast with on average 30 % homology. Different clades of RBPs display varied degrees of conservation. Cytosolic ribosomal proteins are the most conserved with ~57 % homology, while proteins associating

with mRNAs or ncRNAs are least conserved, 27 % and 20 %, respectively, and also have the least number of conserved homologs, 45 % and 21 %, respectively (Fig. 1.3c). Nevertheless, despite the gene expansions within protein families at later evolutionary stages (Venter 2001; Van de Peer et al. 2009), the relative ratios of paralogous RBPs families invested in the different RNA pathways remain approximately the same across evolution as seen for the distribution between human and yeast RBP families (Fig. 1.3b, c). This breadth of PTGR factors agrees with an earlier analysis of 32 RBP domain classes of canonical RBDs (including RRM, KH, dsrm, DEAD, PUF, Piwi, PAZ, zinc finger, LSM) showing that the large diversity of RBPs found in contemporary metazoans was already established in the last common ancestor (LCA) of animals, and which possessed an estimated total number of 88 RRM, 15 KH, 49 DEAD box, 9 dsrm, and 38 other RBD proteins (Kerner et al. 2011). Thus the complexity of PTGR was present at the earliest stages of evolution, reflecting that RNA metabolism lies at the heart of eukaryotic gene regulation.

Visualization of the evolutionary relationships of RBP families facilitates systems biology approaches to dissect their regulatory roles. Phylogenetic trees give an intuitive graphic representation of the conservation of proteins, highlight closely related homologs, and thereby provide a glimpse into function of uncharacterized RBPs if function has been already established for a relative. Phylogenetic comparison of the predominantly mRNA-binding KH-domain-containing proteins and the proteins of the small subunit of the cytosolic ribosome illustrates the differences in their evolutionary trajectory (Fig. 1.4).

KH proteins experienced multiple gene expansions, as noted earlier for mRBPs, and evolved new RBP families at the later metazoan stages, thereby expanding and diversifying components involved in various regulatory pathways, such as mRNA splicing, translational regulation, and transport. KH protein families contain between one and four members in human, and possess generally one distantly related homolog in yeast (Fig. 1.4a). Multiple family members often have redundant biological functions and RNA target spectra. For example, members of the FMR1 family (FMR1, FXR1, FXR2) or the IGF2BP1 family (IGF2BP1, 2, and 3) show >90 % identical RNA-binding specificities (Hafner et al. 2010; Ascano et al. 2012).

In contrast, cytosolic ribosomal proteins display an unusually high conservation, not too surprising, given that the process of protein translation is conserved to such a high degree between prokaryotes and all clades of eukaryotes that functional details of translation determined in bacteria are almost identical to higher systems (Wool et al. 1995; Melnikov et al. 2012; Dever and Green 2012). The ~90 human ribosomal cytosolic proteins are highly similar in structure and function between yeast and human and show late divergence in evolution, as illustrated for the phylogenetic tree of small ribosomal subunit proteins (Fig. 1.4b). With on average 57 % protein identity, all human cytosolic ribosomal proteins have direct one-to-one, or due to a whole-genome duplication in yeast, one-to-two or two-two matching homologs (Wool 1979; Wool et al. 1995; Anger et al. 2013). In contrast, the majority (80 %) of the ~80 human mitochondrial ribosomal proteins (Matthews et al. 1982) have no homologs in yeast, and the few that are conserved have comparatively low homology (22 % identity), reflecting that mitochondrial ribosomes, acquired through

eubacterial endosymbiosis, rapidly evolved independently across species and that major remodeling events happened later in evolution (Cavdar Koc et al. 2001; O'Brien 2003).

5 Structural Analysis of RNA-Binding Domains

Analysis of structural features in proteins and the grouping of proteins into domain classes can help to understand their biological function (Henikoff et al. 1997; Anantharaman et al. 2002). Structural domains can predict how RBPs recognize and bind RNAs. It can also uncover redundancies to other RBPs in target recognition, as well as highlight families of RBPs that remain to be characterized. The size of a domain class mirrors its diversity and evolutionary adaptation to biological pathways.

Structure-guided searches can be valuable to place proteins into biological pathways and, for instance, DICER1 and DROSHA were identified as the endonucle-ases responsible for double-stranded RNA (dsRNA) processing in microRNA (miRNA) maturation based on known structure and substrate preferences of the dsRNA-processing bacterial and yeast RNase III enzymes (Hammond et al. 2000) (Bernstein et al. 2001; Lee et al. 2003). Similarly, the structural similarity of AGO proteins and the germline-specific PIWI proteins sparked the search for PIWI- interacting small RNAs with similar features as miRNAs, now known as piRNAs (Girard et al. 2006; Grivna 2006; Aravin et al. 2006).

For a review of the structural features of RBPs, we analyzed characteristic domain combinations of RBD classes (Fig. 1.5a) and will give here a brief overview over the abundant RBD classes and their modes of RNA-binding, natural targets, and the processes they are involved in. For excluded classes, we refer to a number of excellent review articles (Burd and Dreyfuss 1994; Sommerville 1999; Aravind and Koonin 2001a; Aravind and Koonin 2001b; Anantharaman et al. 2002; Arcus 2002; Szymczyna et al. 2003; Kim and Bowie 2003; Maraia and Bayfield 2006; Lunde et al. 2007; Rajkowitsch et al. 2007; Glisovic et al. 2008; Curry et al. 2009; Mihailovich et al. 2010; Zhang et al. 2010). To give additional insight into the structural properties of RBPs, we distinguished between RBDs with only RNA-binding properties (nonenzymatic RBDs), and RBDs that also contain enzymatic functions (enzymatic RBDs), such as RNA helicases, ATPases, polymerases, editing enzymes, and nucleases.

5.1 Modes of RNA Interaction by RBPs and their Domain Organization

Prototypical single-stranded RNA (ssRNA)-binding domains interact with their targets in a nucleobase-sequence-specific manner typically binding between 4 and 8 nucleotides (Singh and Valcarcel 2005; Lunde et al. 2007; Glisovic et al. 2008). Specificity is introduced mainly by hydrogen bonding and van der Waals interactions of the nucleobases with the protein side chains or the carbonyl and amide groups of the main chain (Auweter et al. 2006), often leaving the RNA phosphate backbone exposed to the solvent. Additional base stacking interactions with aromatic amino acids or positively charged residues in cationic π interactions serve to increase affinity. Double-stranded RNA (dsRNA)-binding proteins achieve specificity through recognition of shape of RNA secondary structure, such as stem–loops (Masliah et al. 2013). Non-sequence-specific RBDs generally interact with the negatively charged phosphate backbone, leaving the bases exposed to the solvent. To

achieve specificity, these RBPs can interact with cofactors recruiting them to specific targets, as has been observed for many RNA helicases (Rocak and Linder 2004; Auweter et al. 2006).

Many RBDs (but also DNA-binding domains) derive from a few common superfamily folds, such as the oligonucleotidyl transferase fold and the oligosaccharide-binding fold (OB-fold). Oligonucleotidyl transferase fold proteins include enzymatic RBPs such as TUTases, polyA polymerases, RNA ligases, tRNA CCA-adding enzymes, and immune-stimulatory 2′, 5′-oligoadenylate synthases (Kuchta et al. 2009). RBDs of the OB-fold superfamily are the S1, PAZ, and CSD domains (Murzin 1993; Arcus 2002; Lunde et al. 2007). However, RBDs largely diversified throughout evolution and most RBD classes have only one member, while only 4 % of all RBD classes found in human have more than eight members. Members of the 26 most abundant RBD classes (with 9 and more members) constitute a third of the 1,542 curated RBPs (Fig. 1.5a); most of them are mRBPs. Some of the highly studied RBDs (Lunde et al. 2007), such as the PUF (two proteins), S1, CSD, and PIWI domains (eight members each), define smaller RBD classes in humans. Particularly, ribosomal structural components and proteins involved in processes related to ribosome maturation are unique and thus cannot be classified into large families of related structural organization (Korobeinikova et al. 2012).

More than half of all RBPs contain only one RBD; mRBPs, however, form a notable exception and often have multiple RBDs, either one repeated RBD or multiple RBDs in combination. This modular design allows flexibility and versatility for target recognition and, as RBDs usually recognize relatively short stretches of RNA, increases the affinity and specificity for RNA targets by extending the RNA recognition element (RRE) of the protein (Lunde et al. 2007). A few RBDs are exclusively found in combination with other conserved protein domains, such as RBM1CTR in hnRNPs or the PAZ domain found in the Argonaute proteins and DICER1.

5.2 Abundant Nonenzymatic RBDs

5.2.1 RNA-Recognition Motif—The ssRNA-recognition motif (RRM) is the most frequently found RNA-binding domain in eukaryotes, and has 226 members in humans. The ~90 amino-acid-long domain adopts a βαββαβ topology and is composed of two RNP consensus motifs that recognize 4–6 nucleotides (nts) by stacking interactions of the bases with three conserved aromatic amino acids in the β-sheets (Auweter et al. 2006; Lunde et al. 2007; Cléry et al. 2008). Its small size and modular organization yield flexibility to adaptive change and allowed the RRM domain to vastly expand during evolution (Anantharaman et al. 2002).

Deviations from this canonical binding mode, including N- and C-terminal extensions of the domain, as well as usage of the linker regions and other regions outside of the β-sheet, have been characterized and allow for recognition of up to 8 nt (Maris et al. 2005; Auweter et al. 2006; Lunde et al. 2007; Cléry et al. 2008; Muto and Yokoyama 2012).

Sixty-one RRM proteins only comprise a single isolated RRM domain; examples include the polyA-binding protein CPEB family and the nuclear cap-binding protein NCBP2 (CBP20)

(Fig. 1.5b). Sixty RBPs occur with several repeated RRMs; among them are the PTBP and the ELAVL families, regulators of mRNA splicing, stability, and localization (Sawicka et al. 2008; Simone and Keene 2013). Another 68 RRM proteins are found in combination with other RBDs; prominent examples in this group include the IGF2BP1 and FUS families, involved in translational regulation, mRNA transport, and splicing (Tan and Manley 2009; Bell et al. 2013) (Fig. 1.5b). Hence, RRM proteins are found in a variety of biological pathways, the majority of which involve mRNA-related processes, such as regulation of mRNA stability, splicing, translation, and transport. RRM domains are generally a diagnostic indicator for ssRNA binding. In a few cases, however, protein-binding partners have been shown to occlude interaction of the RRM domain with RNA, as seen for the RRM domain of the exon junction complex protein RBM8A (Y14), which binds to the protein cofactor MAGOH (Maris et al. 2005; Glisovic et al. 2008).

5.2.2 K-Homology Domain—The heterogeneous nuclear RNP K-homology (KH) domain binds to ssRNA and ssDNA, and has 39 members in humans. KH domains are ~70 amino acids long and characterized by a hydrophobic core domain with an (I/L/V)IGXXGXX(I/L/V) consensus sequence in the center. Structurally, all KH domains form a three-stranded β-sheet packed against three α-helices and belong either to the eukaryotic type I, of βααββα topology, or the prokaryotic type II, of αββααβ topology (Grishin 2001; Lunde et al. 2007; Valverde et al. 2008). KH domains typically recognize 4-nt ssRNA sequences through electrostatic interactions. Signal transduction and activation of RNA (STAR) proteins, such as SAM68 and QKI, contain just a single KH domain sandwiched between two short signaling motifs, which modulate the protein activity through posttranslational modifications in response to intracellular signaling pathways (Lasko 2003; Chénard and Richard 2008). However, most KH proteins contain combinations of RBDs including the IGF2BP1 family, with four KH and two RRM motifs (Bell et al. 2013), and the brain-specific NOVA splicing family with three repeated KH domains (Li et al. 2007) (Fig. 1.5b). The most extreme example of multiplication of RBDs is found in HDLBP, conserved from yeast to humans, which has 14 repeated KH domains in human (Fig. 1.5b). Analogous to RRM proteins, KH domain proteins predominantly interact with mRNAs and are found in posttranscriptional processes, such as mRNA splicing (PCBP and NOVA family), transport, and translation (IGF2BP1, FMR1, and the MEX family). The two, highly conserved, KH domain proteins PNO1 and RPS3 represent an exception in their target specificity and interact with rRNA during ribosome biogenesis (Vanrobays et al. 2004; Anger et al. 2013).

5.2.3 Double-Stranded RNA-Binding Motif—The dsRNA-binding motif (dsrm) has 21 members and 4 dsrm-like members in humans. Dsrm domains are ~70 amino acids long and adopt an αββββα topology, in which the two α-helices are packed against the three β-sheets. This facilitates nonspecific, shape-dependent contacts with the RNA backbone along the minor and major grooves of A-form dsRNA helix, as well as base contacts along the minor groove and the apical loop (Chang and Ramos 2005; Lunde et al. 2007; Masliah et al. 2013). Dsrm domains are rarely found alone; 24 of the 25 of human dsrm proteins contain multiple dsrm domains or other enzymatic and nonenzymatic RBDs that modulate their function. While the best known dsrm-containing proteins are the Staufen family (STAU1, STAU2) of

mRNA stability and transport regulators (Miki et al. 2005; Park and Maquat 2013), this domain type is not confined to mRBPs; instead, most dsrm proteins interact with a range of RNA substrates and are commonly found in RNA enzymes. Members include the adenine-to-inosine RNA-editing ADAR family, processing stem–loops or double strands in mRNAs, viral RNAs, and miRNA precursors (Savva et al. 2012), the two miRNA-processing endonucleases DROSHA and DICER1 (Kim et al. 2009; Wilson and Doudna 2013), as well as the interferon-inducible protein kinase EIF2AK2 (PKR), which, upon binding dsRNA, activates its kinase domain (Saunders and Barber 2003; Raven and Koromilas 2008) (Fig. 1.5b).

5.2.4 CCCH and CCHC Zinc Fingers—The two ssRNA-binding zinc fingers (zf), zf-CCCH and zf-CCHC, form rigid structures by coordination of a Zn^{2+} ion with three cysteine (C) and one histidine (H) residues. In humans, 45 genes contain the zf-CCCH (C-×8-C-×5-C-×3-H type) and 21 contain the zf-CCHC (C-×2-C-×4-H-×4-C) motif, also known as zinc knuckle. Zf proteins form sequence-specific interaction with RNAs through hydrogen bonding and van der Waals interactions of the protein backbone (Lunde et al. 2007; Kaymak et al. 2010), and use stacking interactions of aromatic side chains with the bases to increase RNA-binding affinity. In contrast to other ssRNA-binding domains, the rigidity and shape of the protein structure are the key determinant for specificity of zinc-finger proteins to their target RNAs. The domains generally occur in repeats or in combination with other RBDs. While for most of the CCHC and CCCH zf proteins the molecular function remains unclear, characterized zf proteins are predominantly involved in regulation of mRNA-related processes. Classic examples of zf-CCCH proteins are the AU-rich-binding ZFP36 (TTP) proteins, which participate in rapid degradation of mRNAs transcribed after immune stimulation (Sandler and Stoecklin 2008; Brooks and Blackshear 2013), and the muscleblind (MBNL1,2,3) family, which regulates alternative splicing during muscle differentiation (Pascual et al. 2006; Cooper et al. 2009). Characterized zf-CCHC proteins include the CPSF4 mRNA polyadenylation and cleavage factor (Colgan and Manley 1997; Shatkin and Manley 2000; Proudfoot and O'Sullivan 2002; Proudfoot 2004) (Fig. 1.5b), and the ZCCHC7 (AIR1) protein, member of the nuclear polyadenylation TRAMP complex, required for the degradation of aberrant nuclear ncRNAs (Anderson and Wang 2009). Another prominent member in this class is the LIN28 family (Fig. 1.5b), which posttranscriptionally maintains pluripotency in early embryonic development by inhibiting maturation of miRNA let-7 family precursors and increasing stability and translation of mRNA targets (Thornton and Gregory 2012; Wilbert et al. 2012; Cho et al. 2012; Hafner et al. 2013).

5.2.5 LSM Domain—The LSM domain is found in 19 proteins in humans. First discovered in Sm proteins, it later was re-named LSM ("like-Sm") to include proteins outside of its founding members. The LSM fold is a bipartite domain that stretches along a region of ~65 amino acids and folds into an N-terminal α-helix followed by a twisted five-stranded β-strand (Wilusz and Wilusz 2005; Tharun 2009). The two motifs, motif I, ~22 residues long, and motif II, ~16 residues long, are connected by a variable linker region. LSM proteins form hexa- and heptameric-ring-shaped complexes around RNA. Binding to short, internal polyU- and polyA-rich stretches, they generally associate with snRNAs and

some snoRNAs to form stable snRNP complexes (Achsel et al. 2001; Khusial et al. 2005). These RNP complexes commonly act as RNA-RNA and RNA-protein chaperones (Wilusz and Wilusz 2005; Tharun 2009).

The originally characterized Sm proteins (SNRPB, SNRBPD1, SNRBPD2, SNRBPD3, SNRBPE, SNRBPF, SNRBPG) form the core protein complex around the snRNAs of the major and minor spliceosome (U1, U2, U4, U5, U11, U12, U4atac) (Tharun 2009). Other combinations of LSM-fold proteins and their RNA components lead to functional complexes (Beggs 2005; Wilusz and Wilusz 2005; Tharun 2009), such as the nuclear LSM2-8 protein complex (LSM2, LSM3, LSM4, LSM5, LSM6, LSM7, LSM8), which forms around U6 and U6atac snRNA and participates in mRNA splicing. Association of the same LSM proteins around the C/D box U8 snoRNA results in an RNP complex functioning in rRNA maturation (Pannone et al. 2001; Tomasevic and Peculis 2002). In addition, binding of LSM2-8 to nuclear polyadenylated mRNAs promotes mRNA decapping (Kufel et al. 2004). Other LSM complexes include the U7 snRNP complex (SNRPB, LSM10, SNRPD3, LSM11, SNRPE, SNRPF, SNRPG), which is essential for histone 3′end processing (Pillai et al. 2001), and the cytoplasmic LSM1-7 complex (LSM1, LSM2, LSM3, LSM4, LSM5, LSM6, LSM7), which localizes to P bodies and facilitates mRNA decapping after deadenylation (Tharun et al. 2000; Coller and Parker 2004; Parker and Song 2004; Parker and Sheth 2007). We can expect the identification of novel functions and target specificities in PTGR by as yet uncharacterized variations in the composition of LSM complexes (Wilusz and Wilusz 2005).

5.2.6 PIWI and PAZ Domain—The combination of PIWI, PAZ, and MID domains characterizes the Argonaute RBP family, a clade wirh four AGO and four PIWI protein members in humans (Peters and Meister 2007; Kim et al. 2009). Proteins of this clade bind miRNAs, siRNAs, and piRNAs by anchoring the 5′ phosphate in the MID-domain pocket and the 3′end in the PAZ domain, while the PIWI domain interacts with the RNA backbone (Song 2004; Song and Joshua-Tor 2006; Wang et al. 2008b; Tian et al. 2011; Simon et al. 2011; Schirle and MacRae 2012). The PAZ RBD is also a structural component of the miRNA-processing endonuclease DICER1 (Zhang et al. 2004).

The 110 amino-acid-long PAZ domain consists of a β-barrel followed by an αβ-domain, and is structurally related to OB folds, S1, and LSM domains (Lunde et al. 2007). Forming a clamp-like structure, the PAZ domain selectively binds the two-nucleotide overhangs of small RNA duplexes at the 3′end, thereby acting as an anchor to position small RNAs for cleavage (Jinek and Doudna 2009). The PIWI domain is structurally similar to the RNase H endonuclease domain; however, in mammals, only PIWI proteins (Siomi et al. 2011) and AGO2 (Meister et al. 2004; Liu 2004) display nuclease activity, while in other AGO proteins subtle changes in the active site or the N-terminal regulatory domain prevent catalytic activity (Hauptmann et al. 2013; Faehnle et al. 2013; Nakanishi et al. 2013). AGO proteins initiate, guided by miRNAs and siRNAs, posttranscriptional silencing of mRNAs (Hutvagner and Simard 2008), and PIWI proteins, guided by piRNAs, silence transposons at the posttranscriptional and epigenetic levels (Kim et al. 2009; Siomi et al. 2011). Given the variability of possible guide RNA sequences, Argonaute proteins are tremendously versatile and by using different endogenously expressed guide RNA sequences they can form

hundreds of distinct RNP complexes in vivo. Capable of targeting virtually any given cytosolic RNA sequence in a specific manner, they are used extensively as a tool in biotechnological applications (Dorsett and Tuschl 2004).

5.2.7 PUF Repeat—In humans, PUF repeats are only found in the two members of the Pumilio family; however, the structure and RNA-recognition mechanism of this domain are highly conserved and probably the best understood among all RBDs. PUF domains are ~40 amino acids long and consist of three α-helices that pack together into a half-ring structure. Each PUF domain recognizes only one nucleotide, but multiple repeats additively increase the number of bases recognized, and Pumilio proteins contain multiple PUF repeats that recognize highly sequence-specifically stretches within mRNAs (Wang et al. 2001). The extremely high specificity is achieved by hydrogen bonding interactions of two residues per repeat, while aromatic side chains wrap the bases into a tight fit. Human Pumilio proteins (PUM1, PUM2) contain eight PUF repeats, which together recognize the sequence UGUANAUA frequently located within the 3′UTRs of its targets to regulate mRNA stability and translation (Wickens et al. 2002; Wang et al. 2002; Hafner et al. 2010). Compared to other RBDs recognizing short and often degenerated RNA sequences, the RRE of Pumilio repeats is highly predictive for identifying Pumilio protein targets. Indeed, predictions of conserved RREs within 3′UTRs of mRNAs mainly identified, next to miRNA, Pumilio protein-binding sites (Xie et al. 2005), highlighting the exceptionally high information content of the Pumilio RRE. The high molecular specificity of the interaction has allowed engineering of RNA-binding specificity of Pumilio proteins to recognize different sequences (Cheong and Hall 2006).

5.3 Predominant Enzymatic RNA-Binding Domains

5.3.1 DExD/H helicases—DExD/H helicases, comprising DEAD and DEAH box helicases, are ATP-dependent enzymes that are involved in RNA-protein remodeling in the cell. They form the second largest class of RBPs comprising 73 members in humans, of which 62 interact specifically with RNA, and the remaining with DNA. The majority of the human RNA-binding DexD/H helicases, 42 members, belong to the DEAD box class, while the others are DEAH and DExH Ski-like helicases (named after its founding member Ski2p) (la Cruz et al. 1999). DExD/H RNA helicases belong to the SF2 helicase superfamily and contain NTPase characteristic Walker A and B motifs; their seven helicase signature motifs extend over ~400 amino acids (Tanner and Linder 2001; Rocak and Linder 2004; Pyle 2008; Jankowsky and Fairman-Williams 2010; Fairman-Williams et al. 2010). The helicases are differentiated by their catalytic core residues Asp-Glu-Ala-Asp for DEAD box helicases, and Asp-Glu-Ala/x- His for the related DEAH box and Ski2-like helicases. The enzymatic core arranges into two discrete domains connected by a linker that forms a cleft, in which an ATP can bind (Tanner and Linder 2001), whose hydrolysis provides the energy for unwinding RNA secondary structures or reorganizing RNPs in either a directional (DEAH helicases) or a bidirectional (DEAD helicases) manner. DExD/H RNA helicases generally lack substrate specificity, or even affinity, towards RNA and DNA. This allows them to promiscuously unwind and remodel a broad range of targets, but also requires their association with cofactors that give specificity and affinity for their targets (Rocak and Linder 2004; Jankowsky and Fairman-Williams 2010). While most members of DExD/H

helicases are involved in mRNA-related processes, in particular splicing, they play essential roles in diverse PTGR pathways such as transcriptional regulation, rRNA and tRNA maturation, viral defense, miRNA RISC loading, translation initiation, RNA export, and degradation (Rocak and Linder 2004; Fukuda et al. 2007; Pyle 2008; Jankowsky 2011; Linder and Jankowsky 2011; Martin et al. 2013; Schmidt and Butler 2013; Fullam and Schröder 2013). Next to RNA-RNA and RNA-protein remodeling, DExD/H helicases are also important in RNA-protein complex disassembly and facilitate removal of protein interactors from their targets during RNA export (Linder and Jankowsky 2011).

Paralogs within one RBP family can function in highly diverse roles and pathways, but even one helicase can assume a variety of different biological functions depending on its associated cofactors. For instance, EIF4A1, the first DEAD box helicase for which remodeling and unwinding was mechanistically characterized, forms the EIF4F translation initiation complex, together with the cap-binding protein EIF4E and the scaffolding protein EIF4G (Gingras et al. 1999; Andreou and Klostermeier 2013). Complexed with EIF4H or EIF4B cofactors, EIF4A1 unwinds secondary structures in the 5′UTR, allowing binding of the 43S ribosome complex for AUG start codon scanning. In contrast, although structurally very similar (65 %), the family member EIF4A3 is a core component of the exon junction complex (EJC), in which it acts as an RNA clamp to assist correct positioning of the EJC 20–24 nt upstream of mRNA exon-exon junctions (Linder and Fuller-Pace 2013).

5.3.2 EF-Tu GTP-Binding Domain—The EF-Tu GTP-binding domain (GTP_EFTU), named after its prokaryotic founding member EF-Tu, is a highly conserved domain across all kingdoms of life, and shared by 21 genes in humans. The domain is typically found in GTP-binding translation elongation factors, which are composed of three structural domains, the GTP- binding domain, and two β-barrel nucleotide-binding domains, D2 and D3, which bind to aminoacylated tRNAs (Nissen et al. 1995; Wang et al. 1997; Negrutskii and El'skaya 1998). Eukaryotic EF-1α (human ortholog EEF1A1) has also been shown to interact with higher molecular weight G/U-rich RNAs and rRNAs at a tRNA- independent binding site (Negrutskii and El'skaya 1998). Translation elongation factors are essential for protein synthesis; they bind aminoacyl-tRNAs in a GTP- dependent manner and direct them to the A-site of the ribosome where, upon codon recognition by the tRNA, GTP is hydrolyzed and the factor released (Dever and Green 2012). Furthermore, the GTP_EFTU domains are not only found in combination with D2 and D3 in various translation initiation and release factors, but also alone in GTPases involved in mRNA splicing (EFTUD2) (Fabrizio et al. 1997) and rRNA biogenesis (GNL3 family) (Du et al. 2006; Kressler et al. 2010). The biological role for a majority of the human GTP_EFTU-containing proteins has not been characterized. Particularly, the translation-independent roles of EF1-α and family members, which have been found to directly interact with stem–loops in β-actin (ACTB) and metallothionein 1 (human orthologs MT1 family) mRNAs, are not well understood (Liu et al. 2002; Mickleburgh et al. 2006). More than half of the GTP_EFTU-containing proteins were isolated from direct mRNA-cross-linking experiments by Castello et al. (Castello et al. 2012), supporting a wider role for these proteins in PTGR.

6 Tissue Specificity of RNA-Binding Proteins

Given the evolutionary conservation of RBPs and their involvement in general RNA metabolism, one anticipates predominantly ubiquitous expression for the majority of RBPs. Most tissue-specific proteins evolved recently and have ancestral proteins with low conservation, or no homologs in lower eukaryotes (Winter et al. 2004). Hence, tissue-specific RBPs evolved at later stages of metazoan evolution, the most extreme example of which is represented by the vertebrate-specific secreted RNA ribonucleases A (RNase A) family comprising eight nucleolytic and five inactive pseudo-nuclease members (Rosenberg 2011). Among the active members of this class are angiogenin (ANG), which promotes blood vessel growth, cleaves tRNAs under oxidative stress and is predominantly expressed and secreted from the liver, as well as the EDN and ECP RNases (RNASE2 and RNASE3), which play a role in innate immune response and are expressed in bone marrow eosinophiles (Yamasaki et al. 2009; Rosenberg 2011; Ivanov et al. 2011) (Fig. 1.6a).

In order to obtain an overview of the number of tissue-specific RBPs, we examined mRNA expression levels across tissues, which provide a reliable estimate of protein abundance in the cell (Guo et al. 2010). Current RNA-seq resources do not provide a comprehensive collection of tissues profiled in one study and thus we used a publically available microarray tissue atlas comprising 31 different human tissues to examine the tissue specificity of ~17,000 profiled genes (Dezso et al. 2008). We devised a metric measuring tissue specificity by calculating the deviation for each gene from a uniform expression across all tissues. Our analysis likely underestimates tissue specificity, particularly of low-expressed genes, due to tissue heterogeneity, which adds additional noise to the true expression profiles. In addition, mRNA splicing or alternative polyadenylation events, which can give rise to cell-type-specific protein isoforms with different biological functions (Black 2000; Kornblihtt et al. 2013) (Matlin et al. 2005; Sandberg et al. 2008; Mayr and Bartel 2009; Hogg and Goff 2010), cannot be captured by microarray analysis. Nevertheless, a few general themes contrasting RBPs from other protein-coding genes emerge from the present analysis.

About 90 % of the curated RBPs (~1,400) were profiled in the study. While RBPs showed similar average expression levels as compared to other protein-coding genes, they displayed markedly lower variation of expression across tissues. Only ~2 % of RBPs showed very high, tissue-specific expression on the mRNA level compared to 8 % among other protein-coding genes (Dezso et al. 2008). Even when setting the criteria for tissue-specific expression more lenient to include known RBPs with enrichment in selected tissues, only about ~6 % of RBPs were classified as tissue specific, while at the same threshold 20 % of non-RNA-binding proteins displayed tissue-specific expression (Fig. 1.6b, c). Tissue-specific RBPs were predominantly located to the germline, and to a lesser degree to brain, bone marrow, liver, and muscle, where they play distinct biological roles in RNA metabolic pathways (Fig. 1.6a).

RNA metabolism in the germline is uniquely specialized and many of the exclusively expressed RBPs are involved in the piRNA-induced silencing pathway, comprising piRNA biogenesis as well as their effector components such as PIWI (PIWIL1,2,3,4) and TUDOR proteins, MOV10L1, Maelstrom, and PLD6 and DDX4 (VASA) (Siomi et al. 2010; Siomi et

al. 2011). Other germline-specific RBPs are the DAZL family (DAZ1,2,3, DAZL, BOLL) and the nanos zinc fingers (NANOS2, NANOS3), both of which are regulators of mRNA translation (Parisi and Lin 2000; Brook et al. 2009; Barckmann and Simonelig 2013). Loss of function of these genes commonly results in arrest of germline development and leads to infertility (Yen 2004; Klattenhoff and Theurkauf 2008; Kim et al. 2009; Brook et al. 2009; Thomson and Lin 2009; Siomi et al. 2011; Massart et al. 2012; Ishizu et al. 2012; Lasko 2013).

The brain shows higher levels of alternative splicing, polyadenylation, and editing compared to other tissues, which are required for neuronal development, plasticity, and memory functions (Xu et al. 2002; Yeo et al. 2005; Wang et al. 2008a; Grabowski 2011; Miura et al. 2013). The higher level of posttranscriptional regulation points towards the brain's demand to rapidly adapt to evolutionary pressure and PTGR can be considered a means for accelerating evolution of protein diversity (Xing and Lee 2006). Hence, in particular splicing factors are overrepre-sented among the brain-specific RBPs such as the NOVA family, PTB2, and the neuronal members of the RBFOX and ELAVL families (Li et al. 2007). Dysregulation of these proteins results in defects in neurological function and brain development.

We examined paralogous RBP protein families in further detail and defined three categories for tissue specificity in RBP families: (1) highly tissue-specific RBP families, (2) ubiquitous RBP families containing tissue-specific members that evolved independently to meet cell-type-specific needs, and (3) ubiquitous families wherein the individual members display a gradient of expression in different tissues and cell types.

About 2 % of RBP families fall into the first category and display a high degree of tissue specificity in all of their members, expressed in only one or two tissues. Among them are the DAZL, NOVA, RNase A, and PIWI family.

RBP families in the second category (~3 %) have ubiquitously expressed members and one or two tissue-specific paralogs. Members generally have highly overlapping functions, with the tissue-specific paralogs carrying out similar functions to the ubiquitous paralog. A number of germline-restricted helicases, essential for gametogenesis, belong to this category, including DDX4 and DDX3Y, the RNA export factor DDX25, and the piRNA pathway MOV10L1 helicase, all of which have ubiquitously expressed paralogs (DDX3X paralog of DDX4 and DDX3Y, DDX19A and DDX19B paralog of DDX25, MOV10 paralog of MOV10L) (Abdelhaleem 2005; Tsai-Morris et al. 2010; Frost et al. 2010; Zheng et al. 2010; Lasko 2013). Other RBPs include the AU-rich element- binding, nucleocytoplasmic shuttling ELAVL mRBP family (ELAVL1,2,3,4, also known as HuR,B,C,D) (Brennan and Steitz 2001; Simone and Keene 2013). Tissue-specific paralogs likely fulfill a specific demand in PTGR by potentially regulating an increased abundance or number of RNA targets in this tissue. Several mRBP families, such as the ELAVL family, possess identical RNA-binding specificities (Ascano et al. 2011). Whether ubiquitous paralogs are able to functionally compensate for loss of function of their tissue-specific counterparts has not been evaluated systematically in vivo. However, despite their close homology, overexpression of ELAVL4 but not ELAVL1 in cultured neural crest cells is able

to induce neurite outgrowth (Wakamatsu and Weston 1997), suggesting that, differences in expression levels alone may not fully account for the different biological functions of paralogs.

About 25 % of paralogous families are ubiquitously expressed but their members display some tissue-specific variation in expression. For these proteins, different expression levels in different tissues can reflect a higher demand or sensitivity for the expressed RBP due to different metabolic activities in different cell types. As expected, dysregulation of the RBPs shows the strongest phenotype in the tissues with highest expression. For instance loss of FMR1, expressed ubiquitously in every tissue but found elevated in brain and gonads (Wang et al. 2008a), leads to mental retardation and autism, macroorchidism, and ovarian insufficiency (Ascano et al. 2012). The variations in RBP expression leading to tissue-specific phenotypes may be considered in the selection of suitable model systems for the investigation of their biological function.

The residual 70 % of paralogous RBP families are expressed ubiquitously with marginal variation in expression. Dysregulation of ubiquitous RBPs impacts PTGR in multiple tissues; however, the severity of the phenotype in different tissues varies. Thus, counterintuitively, loss of abundantly and ubiquitously expressed SMN1 leads to spinal muscular atrophy (SMA), and mutation or loss of TARDBP/TDP43 is associated with amyotrophic lateral sclerosis (ALS) (Ule 2008; Lagier-Tourenne et al. 2010). These examples indicate that tissue-specific defects caused by dysregu-lation of an RBP do not strictly correlate with levels of expression and that differences in expression of RNA targets, protein partners, or additional biological roles of the protein must also be taken into consideration. To understand tissue-specific phenotypes of ubiquitous RBPs it may be necessary to also consider the tissue-specific expression levels of RNA targets or protein cofactors.

7 RBPs in Human Disease

Efforts to understand the role and the pathomechanisms of RBPs in disease have focused predominantly on mRBPs (Wang and Cooper 2007; Lukong et al. 2008; Ule 2008; Cooper et al. 2009; Hanson et al. 2011; Kapeli and Yeo 2012; Castello et al. 2013; Ramaswami et al. 2013). Disease associations of RBPs targeting other classes of RNA such as tRNAs, rRNAs, snoRNAs, snRNAs, and others have been less extensively covered (Scheper et al. 2007a, b; Antonellis and Green 2008; Perron and Provost 2009; Narla and Ebert 2010; Wapinski and Chang 2011; Esteller 2011; Batista and Chang 2013). Here we will give a brief overview of RBPs identified as Mendelian disease factors, categorized by targets, and will focus on their characteristic disease phenotypes (Table 1.2).

Despite the interdependence of RNA regulatory pathways, many of the observed disease phenotypes are specific for RBPs binding to particular classes of RNAs, and symptoms of diseases with unknown molecular mechanisms could point towards putative dysregulated RNA metabolic pathways. The majority of RBPs have not been associated with diseases yet, but the recurring patterns occurring for the known proteins may support, facilitated by the

growing genomic and transcriptomic data from patients, the interpretation of the dysregulated pathways involving new candidates in disease.

7.1 Diseases Involving mRNA-Binding Proteins

Most of the ~150 RBPs currently listed in the OMIM database (Hamosh et al. 2005) are mRNA-binding proteins with phenotypes characteristically showing neurological and neuromuscular dysfunctions due to dysregulation of splicing, translation, localization, or protein aggregation (Lukong et al. 2008; Ule 2008; Cooper et al. 2009; Hanson et al. 2011; Kapeli and Yeo 2012). Family members tend to have overlapping phenotypes reflecting functional redundancies; for instance the paralogs RBM20 and MATR3 are both involved in myopathies due to dysregulated splicing of their targets (Senderek et al. 2009; Guo et al. 2012).

RNA gain of function leading to altered mRBP-binding patterns is a common pathomechanism (Cooper et al. 2009; Echeverria and Cooper 2012; Nelson et al. 2013). In these disorders, repeat expansions in introns or UTRs of mRNAs often lead to sequestration of mRBPs in the nucleus, thus causing dysregulation of their respective targets. Such diseases comprise FXTAS (fragile X-associated tremor/ataxia syndrome), caused by trinucleotide repeat expansions in the 5′UTR of the FMR1 mRNA (Hagerman 2013), and the myotonic dystrophies DM1 and DM2, caused by repeat expansions in the 3′UTR of DMPK and the intron of CNBP (ZNF9), sequestering the mRBPs CELF1 and MBNL1 and their paralogs (Echeverria and Cooper 2012).

Mutations leading to prion-like aggregation of cytoplasmic or shuttling mRBPs and the dysregulation in assembly and disassembly processes of cytoplasmic RNP granules have been found to be the underlying cause in a range of neurodegenerative disorders. Cytoplasmic inclusion of TARDBP/TDP43 and FUS has been found in amyotrophic lateral sclerosis, a motor neuron disease leading to muscle atrophy (Anthony and Gallo 2010; Lagier-Tourenne et al. 2010; Lee et al. 2012; Ling et al. 2013). Accumulation and inefficient removal of these RNA-protein granules lead to cellular stress predominantly affecting neuronal cells (Liu-Yesucevitz et al. 2011; Li et al. 2013; Buchan et al. 2013; Ramaswami et al. 2013).

7.2 Mitochondrial RBPs in Disease

mRBPs involved in mitochondrial metabolism, such as translation elongation factors GFM1 and TSFM, typically cause deficiencies in oxidative phosphorylation that manifest themselves on a physiological level as neurological and muscular myopathies (Smeitink et al. 2006). Analogously, defects in mitochondrially localized tRNA- and rRNA-binding proteins and subunits of the mitochondrial ribosome also cause deficiencies in oxidative phosphorylation (Smits et al. 2010; Yao and Fox 2013) (Table 1.2).

7.3 Diseases Involving snRNA-Binding Proteins

Mutation or loss of function of snRBPs involved in snRNP complex formation or snRNA biogenesis causes defects in proper mRNA splicing and affects mRNA splicing patterns. Overall, only a few snRBPs have been linked to disease.

The most studied snRBP is the SMN protein, the loss of function of which causes spinal muscular atrophy (SMA). SMN proteins form a multimeric complex with Gemin proteins, which carries out the assembly of snRNPs and other RNP complexes in the cytoplasm (Paushkin et al. 2002; Battle et al. 2006). Autosomal recessive loss of function of the SMN1 gene is the molecular cause for SMA, affecting 1 in 6,000 births (Gubitz et al. 2004). The pathomechanism of SMA exemplifies a striking example of how a single point mutation within a cryptic splice-enhancer site can lead to dramatically altered protein levels that result in global defects in mRNA splicing. Two copies, SMN1 and SMN2, are found in the human genome encoding identical forms of the mature protein. Transcription from the SMN1 locus gives full-length mRNA. The SMN2 gene, however, harbors a single, silent nucleotide mutation in exon 7 leading to frequent exon skipping and resulting in only a small fraction of functional protein being produced, with the majority of transcripts giving rise to truncated, inactive protein. In the disease, deletion of the SMN1 gene results in the SMN2 locus being the only source for full-length mRNAs and protein. The very low amounts of SMN protein produced lead to highly skewed ratios of snRNPs, resulting in global aberrant splicing patterns (Zhang et al. 2008; Cooper et al. 2009). While snRNP assembly defects are detected in all tissues upon SMN1 deletion, the physiological phenotype manifests itself mainly in motor neurons (Glisovic et al. 2008; Cooper et al. 2009; Liu-Yesucevitz et al. 2011).

Mutations in other snRNP complexes have also been shown to cause disease. Loss of function of snRBPs of the U2, U12, and U4/U6-U5 snRNP complexes specifically cause retinitis pigmentosa, a retinal degeneration leading to blindness caused by incorrect splicing of mRNAs encoding for photoreceptors (Daiger et al. 2013). Why mutations in components of the general splicing machinery display highly tissue-specific phenotypes in the eye remains unclear (Wang and Cooper 2007; Singh and Cooper 2012).

7.4 Diseases Involving tRNA Metabolism of tRNA-Binding Proteins

Disease-causing mutations in tRNA-binding proteins are found in the tRNA maturation and aminoacylation pathways and show predominantly neurological phenotypes (Scheper et al. 2007a, b) (Table 1.2). Mutations in a number of cytoplasmic tRNA synthetases cause Charcot-Marie-Tooth disease, affecting the peripheral nervous system and leading to muscular atrophy (Antonellis and Green 2008; Yao and Fox 2013). Mutations in TSEN tRNA-splicing endonucleases lead to pontocerebellar hypoplasia, a sometimes fatal underdevelopment of the cerebellum, causing intellectual disability and impairing muscle control and motor skills (Budde et al. 2008). Dysfunctions of cytoplasmic tRNA aminoacyl synthetases lead to inefficient translation and molecularly link tRNAs with mRNA-binding proteins (Scheper et al. 2007a, b), explaining the overlapping range of symptoms observed for these classes of RBPs in neurological diseases.

7.5 Diseases Involving rRNA-Biogenesis Factors and Ribosomal Proteins

Loss of function of rRNA biogenesis factors and ribosomal proteins is generally embryonically lethal and only few diseases, classified as ribosomopathies, are known for these RBPs (Ruggero and Pandolfi 2003; Narla and Ebert 2010). Ribosomopathies commonly show growth retardation, organ malformation, and frequently bone marrow

failure (Liu 2006). Examples of ribosomopathies include mutations in the SBDS rRNA biogenesis gene that cause Shwachman-Bodian syndrome, displaying a deficit in neutrophils and other blood cell types (Boocock et al. 2003), as well as a number of ribosomal proteins predominantly belonging to the small ribosomal subunit that cause Diamond-Blackfan anemia, an impairment of red blood cell formation (Narla and Ebert 2010).

7.6 Diseases Involving snoRNA-Binding Proteins

snoRNA-binding proteins are involved in maturation pathways of rRNAs, snRNAs, and the H/ACA-snRNA-like telomerase RNA. Dysregulation of snoRNPs leads to deficiencies in nucleotide modifications, pseudouridylation, or methylation of their targets (Bachellerie et al. 2002; Filipowicz and Pogaci 2002). As a consequence, snoRNP disease phenotypes overlap with those observed for defects in rRNA biogenesis, ribosomal proteins, as well as proteins involved in the telomerase assembly pathway, such as the protein components TERT and WRAP53 of the telomerase complex. Defects in snoRNA biogenesis manifest themselves in the severe developmental disorder dyskeratosis congenita, leading to bone marrow failure, growth retardation, neurological defects, and premature aging (Filipowicz and Pogaci 2002; Smogorzewska and de Lange 2004).

7.7 Diseases Involving microRNA Pathway Components

Mutations in miRNA-binding proteins are involved in different cancers and developmental disorders and have been well characterized (Merritt et al. 2008; Perron and Provost 2009; Kaneko et al. 2011). For example, mutations and loss of function or reduced levels of DICER1, TARBP2, and XPO5 have been found in pleuropul-monary blastomas and ovarian and other types of cancers (Zhang et al. 2006; Melo et al. 2009; Hill et al. 2009; Melo et al. 2010). In addition, changes in miRNA profiles are observed in many more human diseases due to changes in the cellular metabolism, and may prove valuable diagnostic tools, analogous to mRNA expression profiles (Esquela-Kerscher and Slack 2006; Kloosterman and Plasterk 2006; Calin and Croce 2006; Li and Kowdley 2012).

7.8 Immune Stimulatory and Stress-Related Diseases Caused by RBPs

In recent years it has become evident that nucleic acids play a central role in autoimmune and cellular stress-related diseases. Mutations or loss of function in three RNA/DNA nucleases, SAMHD1, the RNase H2 complex, and TREX1, leads to development of the autoimmune disease Aicardi-Goutieres syndrome (AGS), a neurodevelopmental disorder causing white matter abnormalities and cerebral atrophy. Symptomatically, AGS overlaps with the autoimmune disorder systemic lupus erythematosus (SLE) (Crow et al. 2006b). In both cases, a failure to remove accumulating nucleic acids is central to disease development and activates the innate immune system by type I interferon signaling (Atianand and Fitzgerald 2013; Rabe 2013).

The triphosphatase SAMHD1 possesses 3′–5′ exonuclease activity for ssRNA, ssDNA, and DNA/RNA hybrids. Its antiviral and autoimmune-suppressive function has been attributed to its role in the removal of nucleotides and nucleic acids in the cell (Beloglazova et al. 2013). The heterotrimeric RNase H2 complex endonucleolytically cleaves DNA/RNA hybrids and is thought to be required for the removal of Okazaki fragments during DNA

replication (Cerritelli and Crouch 2009; Rabe 2013). Mutations in all three subunits of the RNase H2 complex (RNASEH2A, RNASEH2B, RNASEH2C) have been found to cause AGS (Crow et al. 2006b; Rabe 2013). The 3′–5′ DNA exonuclease TREX1 is implicated in degradation of ssDNA fragments during replication and antiviral defense (Rabe 2013). Mutations in TREX1 are found in AGS patients (Crow et al. 2006a) and TREX1 knockout mice accumulate endogenous retroelements; the accumulating nucleic acids are thought to trigger a subsequent interferon response (Stetson et al. 2008). Interestingly, loss of function of the dsRNA-editing ADAR enzyme has also been shown to cause AGS by an as yet unknown mechanism (Rice et al. 2012).

Many autoantibodies against other RBPs and even RNA have been detected in paraneoplastic syndromes and autoimmune diseases (DeHoratius et al. 1975; Hendrick et al. 1981; Pettersson et al. 1984; Gold et al. 1988; Gelpi et al. 1992; Sakai et al. 1994; Buckanovich et al. 1996). It is thought that dysregulation of RNA clearance mechanisms triggers innate immune responses and leads to apoptosis and release of RBP-RNA complexes into circulation. There these granules mobilize the immune system to develop autoantibodies against self-RNA-protein complexes (Gaipl et al. 2005; Muñoz et al. 2010). The Ro60 complex, consisting of the TROVE2 (Ro60) protein and Y RNAs, was among the first identified targets of autoimmune antibodies in SLE patients was the Ro-RNP particle (Lerner et al. 1981; Hendrick et al. 1981). The Ro60 complex plays a regulatory role in DNA replication and stress response, removing misfolded RNAs, and mice lacking Ro60 develop lupus-like syndromes (Chen and Wolin 2004; Sim and Wolin 2011; Hall et al. 2013). Cleavage of tRNAs and Y RNAs accompanies cellular stress response and apoptosis (Phizicky and Hopper 2010; Nawrot et al. 2011; Hall et al. 2013; Köhn et al. 2013) and these stress-induced small RNA fragments may also act as immune-stimulatory RNAs. Autoantibodies against RBPs associating with these RNAs have been found in serum of SLE patients, stressing the importance of efficient clearance of circulating RNP granules in autoimmune diseases.

Dysfunctional nucleic acid clearance has not only been associated with autoimmune diseases but also with neurological defects of the peripheral nervous system, as seen in loss of function of the RNA exosome component EXOSC3 and RNASET2 (Henneke et al. 2009; Wan et al. 2012), which also acts as a tumor suppressor (Monti et al. 2008). Given the autoimmune-stimulatory role of nucleic acids it is surprising that loss of these general RNA turnover factors more closely resembles loss of mRBPs or tRNA-binding proteins. It will be interesting to understand in mechanistic detail whether the defects caused by these general factors are due to accumulation of RNA or protein aggregates inside the cell, or due to impaired RNA biogenesis pathways.

8 Conclusion

The central role of PTGR in cellular metabolism can be appreciated by considering the large number of proteins interacting with RNA. Over 1,500 of the 21,000 unique human proteins are directly contributing to PTGR. RBPs form many distinct families with few members and human RBPs can be grouped into ~1,100 paralogous families related by 20 % identity.

The complexity of PTGR was established early evolutionary time scales. The lowest common ancestor of metazoans had a set of ~200 RBPs (Kerner et al. 2011), and of the ~1,100 human RBP families ~600 families have homologs in yeast. As a comparison, a census of human and *S. cerevisiae* transcription factors containing transcription factor domains estimated ~1,400 and ~150 genes in human and yeast, respectively (Costanzo et al. 2000; Lee et al. 2002; Vaquerizas et al. 2009). The difference reflects that transcription factors underwent large expansions in the eumetazoan lineage (Larroux et al. 2008; Degnan et al. 2009), suggesting that the rapidly evolved complexity of transcriptional regulation was required for the development of multiple cell types in eukaryotes.

Consistent with their high degree of conservation, most RBPs (98 %) do not display highly tissue-specific expression, but they are abundant and make up to 25 % of the total cellular protein content. Interestingly, dysregulation of ubiquitous and general components in PTGR often shows highly tissue-specific phenotypes; for instance defects involving mRNA- and tRNA-binding proteins are most frequently associated with neurological diseases, especially of the peripheral nervous system.

Given that the common RBD folds have been characterized and the majority of RBPs do not fall into large families, novel RBPs are most probably singular or have recently evolved RNA-binding activity independent of their family. This makes RBP prediction highly challenging and leaves experimental approaches as the most suitable strategy for their identification. Novel genome-wide experimental methods such as covalent RNA-protein cross-linking coupled with high-throughput sequencing to identify RNA target sites, or combined with mass spectrometric approaches to identify proteome-wide RBPs cross-linked to RNAs, have substantially advanced the efforts towards the elucidation of posttranscriptional regulatory networks. With the increasing sensitivity of experimental approaches, the number of RBPs is likely to grow. Even at present though, the precise biological functions and RNA targets for the majority of known human RBPs have not been characterized and some processes, such as noncoding RNA maturation pathways, control of RNA transport, sensing of intracellular RNA, and mechanisms of RNA/RNP clearance, remain poorly understood. Thus, the main challenges in the field are the characterization of these processes and the mechanisms leading to human disease.

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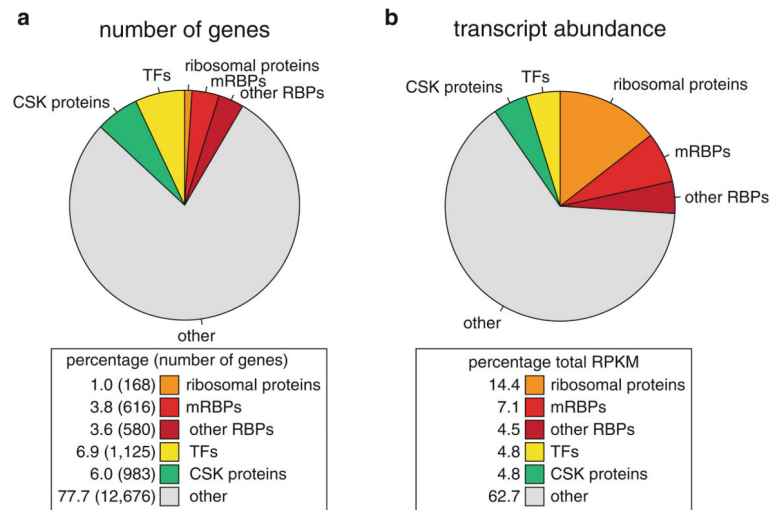
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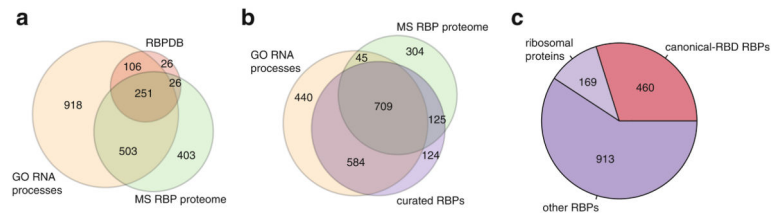
Fig. 1.1.
Different approaches to define the catalogue of human RBPs. (**a**) Venn diagram showing the overlap of proteins with RNA-related Gene Ontology (GO) categories (Ashburner et al. 2000) (*orange*), the human RNA-binding proteome identified by RNA-cross-linking and mass spectrometry studies (MS RBP proteome, *green*) (Baltz et al. 2012; Castello et al. 2012; Kwon et al. 2013), and the RBPDB database of human RBPs with canonical RBDs (Cook et al. 2011) (*red*). (**b**) Venn diagram showing the overlaps of GO RBPs (*orange*), MS RBP proteome (*green*), and the curated RBP list based on analysis of RNA-binding domains and experimental evidence of RNA binding found in the literature (*violet*). (**c**) Composition of RBPs in the curated RBP list: Canonical-RBD RBPs (containing canonical RBDs (Lunde et al. 2007; Cook et al. 2011), *red*), ribosomal proteins (*bright violet*), other RBPs (*dark violet*)

a number of genes

b transcript abundance

percentage (number of genes)

1.0 (168)	ribosomal proteins
3.8 (616)	mRBPs
3.6 (580)	other RBPs
6.9 (1,125)	TFs
6.0 (983)	CSK proteins
77.7 (12,676)	other

percentage total RPKM

14.4	ribosomal proteins
7.1	mRBPs
4.5	other RBPs
4.8	TFs
4.8	CSK proteins
62.7	other

Fig. 1.2.

Analysis of RBP abundance. Curated RBPs are subclassified into ribosomal proteins (*orange*), mRBPs (*bright red*), and other RBPs (*dark red*). Percentages of RBPs are compared to a set of GO-defined transcription factors (TFs, *yellow*), a set of GO-defined cytoskeletal proteins (CSK proteins, *green*) (Ashburner et al. 2000), and all other expressed genes (*grey*). (**a**) Count of expressed genes with RPKM > 1 in RNA-seq data from HEK293 cells (Teplova et al. 2013). (**b**) Relative abundance of each gene group is given by the summation of expression levels of genes in each category

a human RBPs (1,542)

% (number)
11.0 (169)
44.9 (692)
9.9 (153)
7.9 (122)
5.8 (90)
2.7 (41)
7.9 (122)
0.6 (10)
2.4 (37)
6.9 (106)

b human RBP families (1,113)

% (number)
14.2 (158)
38.1 (424)
11.7 (130)
9.6 (107)
6.6 (73)
3.4 (38)
6.9 (77)
0.9 (10)
2.0 (22)
6.6 (74)

c human RBP families conserved in yeast (551)

% (number)   % homology
15.8 (87)   50.8
32.3 (178)   26.8
18.3 (101)   31.1
13.6 (75)   30.8
5.8 (32)   31.8
6.0 (33)   32.3
2.4 (13)   20.3
1.0 (6)   26.2
2.7 (15)   28.6
2.0 (11)   28.3

mRNA-
tRNA-
rRNA-   interacting
snRNA-   proteins
snoRNA-
ncRNA-

ribosomal proteins
RNA/DNA hybrid-binding
diverse (≥ 3 different classes)
unknown targets

Fig. 1.3.

Number of RBPs involved in different RNA pathways. Curated RBPs are categorized into the following groups: (*1*) Ribosomal proteins and RBP-interacting proteins (e.g., TUDOR proteins, RBP transport proteins) (*dark blue*), (*2*) mRNA-binding proteins (*orange*), tRNA-binding proteins (*red*), rRNA-binding proteins (*dark green*), snRNA-binding proteins (*bright green*), snoRNA-binding proteins (*yellow*), ncRNA-binding proteins (ncRNAs defined as miRNA, piRNA, MRP, 7SL, XIST, lincRNAs, telRNA, etc.) (*light grey*), RNA/DNA-hybrid-interacting proteins (*violet*), RBPs interacting unselectively with a range of RNA targets (*light blue*), RBPs with unknown RNA targets (*marine blue*). Distribution into the listed categories of the (**a**) 1,542 curated human RBPs, (**b**) 1,113 human paralogous RBP families, and (**c**) conserved paralogous RBP families in *S. cerevisiae* and their average conservation score (*orange box*)

Fig. 1.4.
Phylogenetic trees of (**a**) KH-containing proteins and (**b**) ribosomal proteins of the small subunit. Branch lengths are scaled to the sequence identity of the proteins. *S. cerevisiae* proteins are marked in *red*, human proteins in *black*, homologous families with conserved members in S. cerevisiae highlighted in yellow
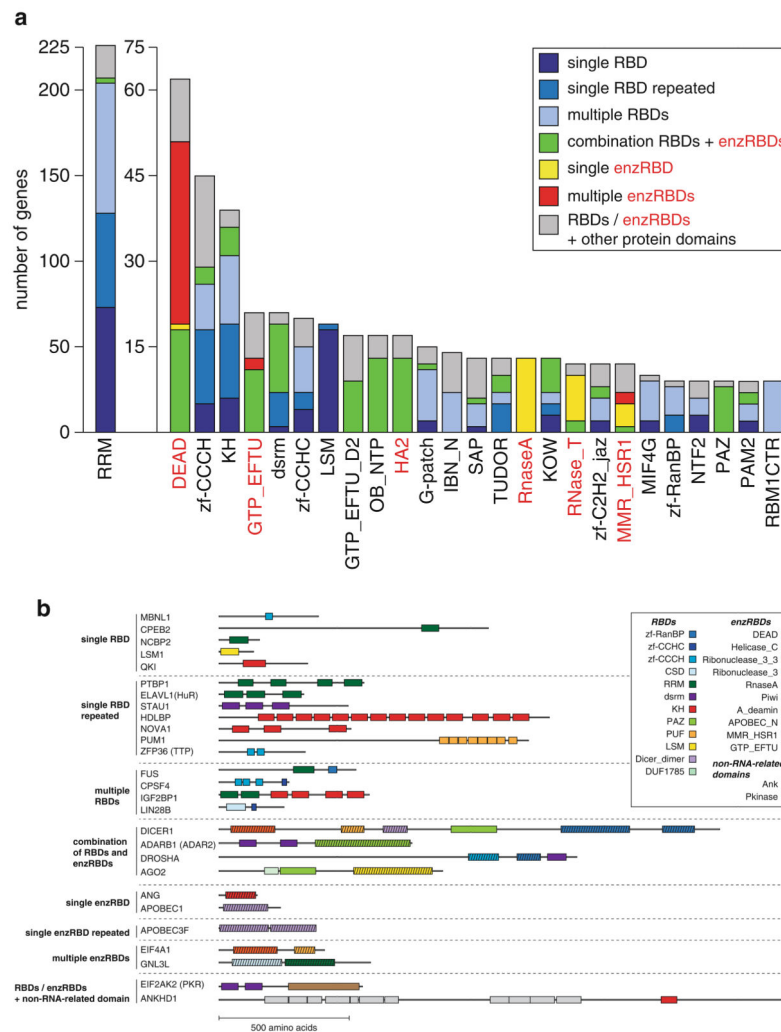
Fig. 1.5.

(**a**) Analysis of structural patterns of the most abundant RNA-binding domains (with 9 members) in humans. Shown are the counts for the number of genes containing the listed RNA-binding domains (with 9 members) named by its Pfam abbreviation (Finn et al. 2010). RNA-binding domains are categorized into those binding RNA without additional enzymatic activity (RBD) (*black*) and those with additional enzymatic activity (enzRBD) (*red*). The RBD category was broadly defined to include protein-protein interacting domains known to interact with RBPs, such as those found in TUDOR family proteins (TUDOR) or ribosomal proteins. The following structural patterns are counted: (*1*) singular occurrence of an RNA-binding domain (RBD—*dark blue*, enzRBD—*yellow*), (*2*) single RBD repeated (RBD—*marine blue*), (*3*) multiple RBDs (RBD—*light blue*, enzRBD—*red*), (*4*) combinations of RBDs and enzRBDs (*green*), and (*5*) combination of at least one RBD/ enzRBD with at least one other, non-RNA-related protein domain (*grey*). (**b**) Scheme of domain structure organization of representative RBPs, categorized into the domain combination classes listed in (**a**)

a tissue specifity of RBPs in relationship to their expression levels

b human RBPs (1,367)

c human proteins (16,867)
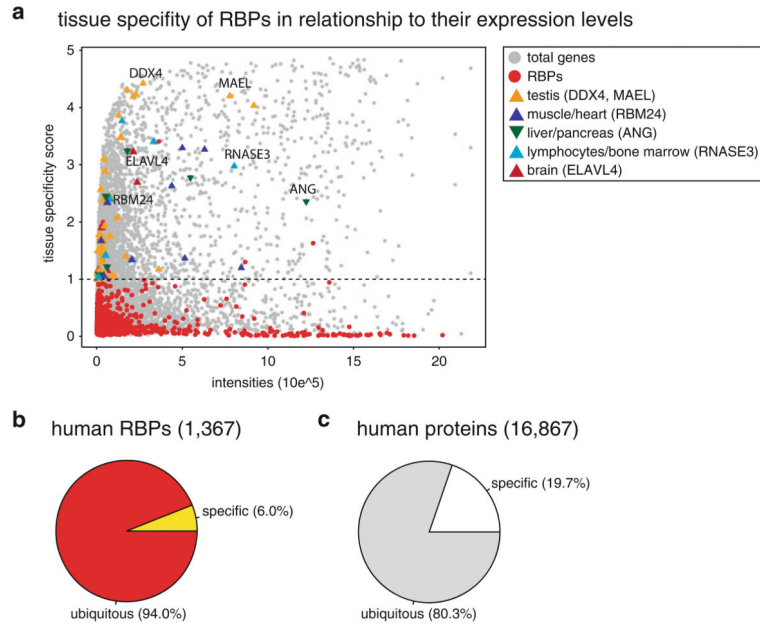
Fig. 1.6.

Tissue specificity of RBPs based on their mRNA expression profiles in a human microar-ray tissue atlas (Dezso et al. 2008). (**a**) Plot of maximum expression intensity versus their tissue specificity score. The threshold for tissue specificity is set at 1 (*dashed line*), to include the brain- specific ELAVL and NOVA splicing factor families and the germline-specific PIWI family. Protein-coding genes are marked as *grey-filled circles* and RBPs as *red-filled circles*. Tissue-specific RBPs are marked based on the tissue with their highest expression: testis (*orange triangle*), muscle/heart (*dark blue triangle*), liver/pancreas (*dark green inverted triangle*), lymphocytes/bone marrow (*light blue triangle*), brain (*dark red triangle*). In (**b**) the number of tissue-specific RBPs is compared to all expressed RBPs and in (**c**) the number of tissue-specific proteins is compared to total expressed proteins

Table 1.1

Functional description of the main RNA classes in humans and their length distribution

RNA class	Size (nt)	Biological role (additional reviews on function and biogenesis)
Messenger RNA (mRNA)	~200–100,000	Encodes the information for protein-coding genes, translated by ribosomes (Dreyfuss et al. 2002; Glisovic et al. 2008; Müller-McNicoll and Neugebauer 2013)
Transfer RNA (tRNA)	~70–95	RNA adaptor molecule, transports amino acids to ribosome and recognizes specific triplet codons on mRNA (Suzuki et al. 2011; Maraia and Lamichhane 2011; Simos and Hurt 1999)
Ribosomal RNA (rRNA)	121–5,072	Structural component of ribosomes (Boisvert et al. 2007; Ciganda and Williams 2011; Granneman and Baserga 2004)
Small nuclear RNA (snRNA)	~70–190	snRNAs U1, U2, U4, U5, U6, U11, U12, U4atac, and U6atac are core components of the spliceosome; U7 snRNA functions in 3′end maturation of histone RNAs (Kiss 2004; Matera et al. 2007)
Small nucleolar RNA (snoRNA) and small Cajal-body-specific RNA (scaRNA)	~50–450	Guide chemical modifications (methylation and pseudouridylation) of rRNAs, snRNAs, and snoRNAs (Filipowicz and Pogaci 2002; Kiss et al. 2006; Matera et al. 2007)
microRNA (miRNA) and small interfering RNA (siRNA)	21–22	Associate with AGO proteins, guide them to target sequences predominantly in the 3′UTRs of mRNAs, induce degradation and translational repression (Bartel 2009; Kim et al. 2009)
piwi-interacting RNA (piRNA)	~28–32	Associates with PIWI proteins; PIWI RNP complexes induce ribonucleolytic cleavage and epigenetic silencing of transposable elements (Kim et al. 2009; Siomi et al. 2011)
Long intervening noncoding RNA (lincRNA), 7SK RNA	>200	Recruits chromatin modifiers and remodeling complexes, modulates transcription by recruitment of protein cofactors to transcription starts sites and enhancers, functions as molecular scaffolds for nuclear RBPs (Batista and Chang 2013; Ulitsky and Bartel 2013); 7SK RNA regulates transcription elongation (Peterlin et al. 2011)
Ribonuclease P/(RNase P) and mitochondrial RNA-processing endonuclease (MRP RNase)	~260–340	Ribonucleolytic RNP complexes that carry out processing of precursor tRNAs, rRNAs, snRNAs, and other noncoding RNAs (Xiao et al. 2002; Jarrous 2002; Ellis and Brown 2009; Esakova and Krasilnikov 2010)
Y RNA	~80–110	Small noncoding RNAs that form an RNP complex with TROVE2 (Ro60) protein and act as RNA chaperones, have a role in DNA replication and immune response (Hall et al. 2013; Köhn et al. 2013)
Signal recognition particle RNA (7SL/SRP RNA)	~300	RNA of the signal recognition particle; the complex recognizes signal sequences of newly synthesized peptides and targets them to the endoplasmatic reticulum (Akopian et al. 2013)
Vault-associated RNA (vtRNA)	~80–120	Small noncoding RNAs, part of the vault RNP complex, involved in drug resistance, downregulate mRNA targets through posttranscriptional gene silencing (Berger et al. 2008)
Telomerase RNA (telRNA)	~450	RNA component of the telomerase complex TERC, which acts as reverse transcriptase and elongates telomerase repeats, TERC is structurally related to box H/ACA snoRNAs (Egan and Collins 2012)

Additional reviews on biogenesis pathways and RBP components interacting with each class of RNA are referenced

Table 1.2

Overview of RBPs with identified genetic disease-causing mutations collected in the OMIM database (Hamosh et al. 2005), categorized into their main RNA target groups Mitochondrially localized proteins are indicated with (mt). Proteins within the same RBP family are written in one line; if family members are also involved in disease they are highlighted in bold; if family members are involved in diseases other than the listed category they are highlighted in bold brown and found elsewhere in a separate category in the table

RBP class	disease category	RBP family	disease	genetic mutation	reference
mRNA-binding	Cancer	**EWSR1, FUS, TAF15**	Ewing sarcoma, soft tissue tumors	Gene fusion	(May et al. 1993; Ichikawa et al. 1994; Panagopoulos et al. 1994; Gill et al. 1995; Panagopoulos et al. 1999)
		TPR	Gastric, thyroid carcinoma, sarcoma	Gene fusion	(Dean et al. 1987; Gonzatti-Haces et al. 1988)
	Muscular/cardiac disease	**CNBP**, ZCCHC13	Myotonic dystrophy	RNA repeat expansion sequesters RBPs	(Liquori et al. 2001)
		MBNL1, MBNL2, MBNL3	Myotonic dystrophy	Sequestered RBP in repeat expansion	(Miller 2000; Mankodi et al. 2001; Fardaei 2002)
		CELF1, CELF2–6	Myotonic dystrophy	Sequestered RBP in repeat expansion	(Timchenko et al. 1996; Roberts et al. 1997)
		MATR3, RBM20	Cardio-/distal myopathy	Missense mutation	(Senderek et al. 2009; Brauch et al. 2009)
		NOL3	Myoclonus	Missense mutation	(Russell et al. 2012)
		PABPN1, PABN1L	Muscular dystrophy	Polyalanine expansion leading to protein aggregation	(Brais et al. 1998)
	Neurological disease	AFF1, **AFF2**, AFF3, AFF4	Mental retardation	Deletion, loss-of-function through repeat expansion in mRNA	(Knight et al. 1993; Stettner et al. 2011)
		ATXN1, ATXN1L	Spinocerebellar ataxia	Polyglutamine expansion leading to protein aggregation	(Orr et al. 1993; Banfi et al. 1994; Servadio et al. 1995)

RBP class	disease category	RBP family	disease	genetic mutation	reference
		ATXN2, ATXN2L	Spinocerebellar ataxia, susceptibility to late-onset Parkinson disease, susceptibility to amyotrophic lateral sclerosis (ALS)	Polyglutamine expansion leading to protein aggregation	(Pulst et al. 1996; Cancel et al. 1997; Gwinn-Hardy et al. 2000; Elden et al. 2010)
		DYNC1H1, DNAH1-11, DNAH17, DYNC2H1	Charcot-Marie-Tooth disease, mental retardation, spinal muscular atrophy (SMA)	Missense mutation	(Vissers et al. 2010; Weedon et al. 2011; Harms et al. 2012)
		UBA1, UBA6-7	Spinal muscular atrophy (SMA)	Missense mutation	(Ramser et al. 2008)
		EIF2B1	Leukoencephalopathy with vanishing white matter	Missense mutation	(van der Knaap et al. 2002)
		EIF2B2	Leukoencephalopathy with vanishing white matter	Missense, nonsense mutation	(Leegwater et al. 2001)
		EIF2B3	Leukoencephalopathy with vanishing white matter	Missense mutation	(van der Knaap et al. 2002)
		EIF2B4	Leukoencephalopathy with vanishing white matter	Missense mutation	(van der Knaap et al. 2002)
		EIF2B5	Leukoencephalopathy with vanishing white matter	Missense mutation	(Leegwater et al. 2001; van der Knaap et al. 2002; Fogli et al. 2002)
		EIF4G1, EIF4G2, EIF4G3	Parkinson disease	Missense mutation	(Chartier-Harlin et al. 2011)
		FMR1, FXR1, FXR2	Fragile X mental retardation syndrome (FXS), fragile X tremor/ataxia syndrome (FXTAS), premature ovarian failure	Deletion, repeat expansion leading to protein loss-of-function (FXS) or RNA-gain-of-function (FXTAS) sequesters RBPs	(Kremer et al. 1991; Devys et al. 1992; Gedeon et al. 1992; Wöhrle et al. 1992; Murray et al. 1998; Hagerman et al. 2001)
		EWSR1, FUS, TAF15	Amyotrophic lateral sclerosis (ALS)	Missense mutation leading to prion-like protein aggregation	(Kwiatkowski et al. 2009; Vance et al. 2009)
		HNRNPA2B1, HNRNPA0, HNRNPAB, HNRNPA1L2, **HNRNPA1**, HNRNPA3, HNRNPD, HNRNPDL	Amyotrophic lateral sclerosis (ALS)	Missense mutation leading to prion-like protein aggregation	(Kim et al. 2013)
		SETX	Amyotrophic lateral sclerosis (ALS)	Missense, nonsense mutation, deletion	(Moreira et al. 2004)

RBP class	disease category	RBP family	disease	genetic mutation	reference
		TARDBP	Amyotrophic lateral sclerosis (ALS)	Missense mutation leading to protein aggregation	(Sreedharan et al. 2008)
		IGHMBP2	Distal spinal muscular atrophy (DSMA1)	Missense mutation	(Grohmann et al. 2001)
		LRPPRC	Leigh syndrome	Missense mutation	(Mootha et al. 2003)
		MECP2	Rett syndrome, X-linked mental retardation	Missense, nonsense mutation, frameshift, deletion	(Amir et al. 1999; Wan et al. 1999; Cheadle et al. 2000; Huppke et al. 2000)
		MTPAP, TUT1	Spastic ataxia	Missense mutation	(Crosby et al. 2010)
		PARK7	Parkinson disease	Missense mutation	(Bonifati et al. 2003)
		PQBP1	Renpenning syndrome 1	Frameshift	(Kalscheuer et al. 2003)
		PRKRA, TARBP2	Dystonia	Frameshift, missense mutation	(Camargos et al. 2008; Seibler et al. 2008)
		RANBP2, RGPD1-6, RGPD8	Acute, infection-induced susceptibility to encephalopathy	Missense mutation	(Neilson et al. 2009)
		RBM28	Alopecia, neurologic defects, endocrinopathy syndrome	Missense mutation	(Nousbeck et al. 2008)
		UPF3A, **UPF3B**	Mental retardation	Frameshift, missense, nonsense mutation	(Tarpey et al. 2007)
		TIA1, TIAL1	Welander distal myopathy	Missense mutation	(Hackman et al. 2012)
		RBFOX1, RBFOX2, RBFOX3	Mental retardation, epilepsy	Deletion, breakpoint	(Bhalla et al. 2004; Martin et al. 2007)
	Neurological/developmental disease	**GLE1**	Lethal congenital contracture syndrome	Splice site mutation, missense mutation	(Nousiainen et al. 2008)
	Developmental disease	**BICC1**	Susceptibility to renal dysplasia	Missense, nonsense mutation	(Kraus et al. 2012)
		EIF2AK1, EIF2AK2, **EIF2AK3**	Wolcott-Rallison syndrome, multiple epiphyseal dysplasia	Missense, nonsense mutation, splice site mutation	(Delépine et al. 2000; Brickwood et al. 2003; Durocher et al. 2006)

RBP class	disease category	RBP family	disease	genetic mutation	reference
		FTO	Growth, developmental delay	Missense mutation	(Boissel et al. 2009)
		MKRN1, MKRN2, **MKRN3**	Central precocious puberty 2	Missense mutation, insertion	(Abreu et al. 2013)
		NR0B1, NR0B2	Congenital adrenal hypoplasia	Deletion, missense mutation	(Muscatelli et al. 1994; Yanase et al. 1996)
		RBM5, RBM6, **RBM10**	TARP syndrome	Frameshift, missense mutation	(Johnston et al. 2010)
		SF3B4	Acrofacial dysostosis	Missense, nonsense mutation, frameshift	(Bernier et al. 2012; Czeschik et al. 2013)
		SKIV2L	Trichohepatoenteric syndrome 2	Missense, nonsense mutation	(Fabre et al. 2012)
	Infertility	BOLL, DAZ1-4, DAZL	Azoospermia	Deletion	(Reijo et al. 1995)
	Metabolic disease	AUH, ECH1, ECHS1, ECHDC2, ECHDC3	3-methylglutaconic aciduria	Nonsense mutation, frameshift, splice site mutation	(IJlst et al. 2002; Ly et al. 2003)
		C12ORF65 (mt)	Combined oxidative phosphorylation deficiency, spastic paraplegia-55 (SPG55)	Frameshift, missense, nonsense mutation	(Antonicka et al. 2010; Shimazaki et al. 2012)
		GFM1 (mt)	Combined oxidative phosphorylation deficiency	Missense, nonsense mutation	(Coenen et al. 2004; Valente et al. 2007)
		TSFM (mt)	Combined oxidative phosphorylation deficiency	Missense mutation	(Smeitink et al. 2006)
		EEFSEC, **TUFM** (mt)	Combined oxidative phosphorylation deficiency	Missense mutation	(Valente et al. 2007)
		SECISBP2, SECISBP2L	Abnormal thyroid metabolism	Missense mutation	(Dumitrescu et al. 2005)
	Hematologic disease	FIP1L1	Spontaneous hypereosinophilic syndrome	Deletion leading to gene fusion	(Cools et al. 2003; Griffin et al. 2003)
		U2AF1, U2AF1L4	Myelodysplastic syndrome	Missense mutation	(Graubert et al. 2012)
	Ophthalmologic disease	TDRD7	Cataract	Frameshift	(Lachke et al. 2011)
	Immunological/skin disease	ADAD1, ADAD2, ADAT, **ADAR**, ADARB1, ADARB2	Aicardi-Goutieres syndrome (AGS), dyschromatosis symmetrica hereditaria 1 (DSH1)	Missense, nonsense mutation	(Miyamura et al. 2003; Rice et al. 2012)

RBP class	disease category	RBP family	disease	genetic mutation	reference
tRNA-binding	Cancer/metabolic disease	ELAC2	Prostate cancer, combined oxidative phosphorylation deficiency	Missense, nonsense mutation, frameshift	(Tavtigian et al. 2001; Haack et al. 2013)
	Muscular/metabolic/hematologic disease	PUS1	Myopathy, lactic acidosis and sideroblastic anemia 1	Missense, nonsense mutation	(Bykhovskaya et al. 2004; Fernandez-Vizarra et al. 2007)
		YARS2 (mt)	Myopathy, lactic acidosis and sideroblastic anemia 2	Missense mutation	(Riley et al. 2010)
	Neurological disease	AARS, AARS2 (mt)	Charcot-Marie Tooth disease	Missense mutation	(Latour et al. 2010; Lin et al. 2011)
		ADAT3	Mental retardation	Missense mutation	(Alazami et al. 2013)
		AIMP1	Hypomyelinating leukodystrophy	Frameshift	(Feinstein et al. 2010)
		YARS	Charcot-Marie Tooth disease	Missense mutation, frameshift	(Jordanova et al. 2006)
		KARS	Charcot-Marie Tooth disease, deafness	Missense mutation, frameshift	(McLaughlin et al. 2010; Santos-Cortez et al. 2013)
		GARS	Charcot-Marie Tooth disease	Missense mutation	(Antonellis et al. 2003)
		CLP1	Microencephalopathy, motor sensory defects	Missense mutation	(Karaca et al. 2014)
		DARS	Hypomyelination with brainstem and spinal cord involvement	Missense mutation	(Taft et al. 2013)
		DARS2 (mt)	Leukoencephalopathy	Frameshift, missense, nonsense mutation, splice site mutation	(Scheper et al. 2007)
		NSUN2	Mental retardation	Nonsense, missense mutation, splice site mutation	(Abbasi-Moheb et al. 2012; Khan et al. 2012)
		FTSJ1	Mental retardation	Frameshift, splice site mutation	(Freude et al. 2004; Ramser et al. 2004)
		RARS, RARS2 (mt)	Pontocerebellar hypoplasia	Splice site mutation, missense mutation	(Edvardson et al. 2007; Rankin et al. 2010)
		SEPSECS	Pontocerebellar hypoplasia	Missense mutation	(Agamy et al. 2010)

RBP class	disease category	RBP family	disease	genetic mutation	reference
		TSEN2	Pontocerebellar hypoplasia	Missense mutation	(Budde et al. 2008)
		TSEN34	Pontocerebellar hypoplasia	Missense mutation	(Budde et al. 2008)
		TSEN54	Pontocerebellar hypoplasia	Missense, nonsense mutation, deletion	(Budde et al. 2008; Cassandrini et al. 2010)
	Developmental disease	EEF2, EFTUD2	Mandibulofacial dysostosis with microcephaly	Splice site mutation, nonsense, missense mutation, frameshift	(Lines et al. 2012; Bernier et al. 2012; Gordon et al. 2012)
	Metabolic disease	EEF2, EFTUD2	Spinocerebellar ataxia	Missense mutation	(Hekman et al. 2012)
		AARS, AARS2 (mt)	Combined oxidative phosphorylation deficiency	Missense mutation	(Götz et al. 2011)
		MTFMT (mt)	Combined oxidative phosphorylation deficiency	Missense, nonsense mutation, deletion	(Neeve et al. 2013; Haack et al. 2014)
		MTO1 (mt)	Combined oxidative phosphorylation deficiency	Frameshift, missense mutation	(Ghezzi et al. 2012)
		EARS2 (mt)	Combined oxidative phosphorylation deficiency	Missense mutation, insertion	(Steenweg et al. 2012; Talim et al. 2013)
		FARS2 (mt)	Combined oxidative phosphorylation deficiency	Missense mutation	(Shamseldin et al. 2012; Elo et al. 2012)
		SARS2 (mt)	Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis	Missense mutation	(Belostotsky et al. 2011)
		TRMU (mt)	Liver failure, deafness	Missense mutation	(Guan et al. 2006; Zeharia et al. 2009)
	Opthalmologic disease/hearing loss	HARS, HARS2 (mt)	Usher syndrome, Perrault syndrome	Missense mutation	(Pierce et al. 2011; Puffenberger et al. 2012)
		LARS2 (mt)	Perrault syndrome	Deletion	(Pierce et al. 2013)
rRNA-binding	Developmental disease	EMG1	Bowen-Conradi syndrome	Missense mutation	(Armistead et al. 2009)

RBP class	disease category	RBP family	disease	genetic mutation	reference
		MURC, **PTRF**, PRKCDBP, SDPR	Lipodystrophy, muscular dystrophy	Frameshift	(Hayashi et al. 2009; Shastry et al. 2010)
		TCOF1	Treacher Collins syndrome 1	Missense, nonsense mutation, deletion, insertion	(Caluseriu et al. 2013; Marszalek et al. 2003; Splendore et al. 2002; Wise et al. 1997)
	Developmental/hematologic disease	SBDS	Shwachman-Diamond syndrome	Frameshift, missense, nonsense mutation	(Boocock et al. 2003; Nakashima et al. 2004)
	Opthalmologic disease	WDR36	Open angle glaucoma	Missense mutation	(Monemi et al. 2005)
snRNA-binding	Neurological disease	SMN1, SMN2	Spinal muscular atrophy (SMA)	Missense, nonsense mutation, frameshift, deletion	(Lefebvre et al. 1995; Cobben et al. 1995; Parsons et al. 1996; Hahnen et al. 1997; Gambardella et al. 1998; Sossi et al. 2001)
	Skin disease	SART3	Porokeratosis	Missense mutation	(Zhang et al. 2005)
		SNRPE	Hypotrichosis	Missense mutation	(Pasternack et al. 2013)
		USB1	Poikiloderma with neutropenia	Deletion, splice site mutation, frameshift	(Volpi et al. 2010; Tanaka et al. 2010)
	Opthalmologic disease	SNRNP200, ASCC3	Retinitis pigmentosa	Missense mutation	(Zhao et al. 2009)
		PRPF3	Retinitis pigmentosa	Missense mutation	(Chakarova et al. 2002)
		PRPF31	Retinitis pigmentosa	Splice site mutation/deletion, missense mutation	(Vithana et al. 2001)
		PRPF6	Retinitis pigmentosa	Missense mutation	(Tanackovic et al. 2011)
		PRPF8	Retinitis pigmentosa	Missense mutation	(McKie et al. 2001)
		RP9	retinitis pigmentosa	Missense mutation	(Keen et al. 2002)
snoRNA-binding	Neurological disease	NOP56	Spinocerebellar ataxia	RNA repeat expansion sequesters RBPs	(Kobayashi et al. 2011)

RBP class	disease category	RBP family	disease	genetic mutation	reference
	Hematologic/neurodevelopmental/developmental disorder	DKC1	Dyskeratosis congenita	Missense mutation, deletion, intron insertion, splice site mutation	(Heiss et al. 1998; Knight et al. 1999; Vulliamy et al. 1999; Knight et al. 2001; Kanegane et al. 2005; Pearson et al. 2008)
		NHP2	Dyskeratosis congenita	Missense mutation	(Vulliamy et al. 2008)
		NOP10	Dyskeratosis congenita	Missense mutation	(Walne et al. 2007)
cytosolic ribosomal proteins	neurological disease	RPL10, RPL10L	Autism	Missense mutation	(Klauck et al. 2006)
	Hematologic disease	RPL11	Diamond-Blackfan anemia	Frameshift, deletion, splice site mutation, nonsense mutation	(Gazda et al. 2008)
		RPL35A	Diamond-Blackfan anemia	Missense, nonsense mutation, deletion	(Farrar et al. 2008)
		RPL5	Diamond-Blackfan anemia	Missense, nonsense mutation, frameshift, splice site mutation	(Gazda et al. 2008)
		RPS10	Diamond-Blackfan anemia	Missense, nonsense mutation, frameshift	(Doherty et al. 2010)
		RPS17, RPS17L	Diamond-Blackfan anemia	Missense, frameshift	(Cmejla et al. 2007; Gazda et al. 2008)
		RPS19	Diamond-Blackfan anemia	Missense, nonsense mutation, frameshift	(Draptchinskaia et al. 1999; Matsson et al. 1999)
		RPS24	Diamond-Blackfan anemia	Nonsense mutation, frameshift	(Gazda et al. 2006)
		RPS26	Diamond-Blackfan anemia	Missense mutation, splice site mutation, frameshift	(Doherty et al. 2010)
		RPS7	Diamond-Blackfan anemia	Splice site mutation	(Gazda et al. 2008)
mitochondrial (mt) ribosomal proteins	Metabolic disease	MRPL3	Combined oxidative phosphorylation deficiency	Missense mutation	(Galmiche et al. 2011)
		MRPS16	Combined oxidative phosphorylation deficiency	Nonsense mutation	(Miller et al. 2004)
		MRPS22	Combined oxidative phosphorylation deficiency	Missense mutation	(Saada et al. 2007)
lincRNA-binding	Cancer	BRCA1	Breast, ovarian, pancreatic cancer	Missense, nonsense mutation, deletion, frameshift	(Castilla et al. 1994; Simard et

RBP class	disease category	RBP family	disease	genetic mutation	reference
	Neurological disease	**DNMT1**	Cerebellar ataxia, neuropathy	Missense mutation	(Klein et al. 2011; Winkelmann et al. 2012)
	Developmental disorder	EZH1, **EZH2**	Weaver syndrome 2	Missense mutation, frameshift	(Gibson et al. 2012)
miRNA-binding	Cancer	**DICER1**	Pleuropulmonary blastoma, goiter with testicular tumours, embryonal habdomyosarcoma	Missense, nonsense mutation, frameshift	(Hill et al. 2009; Rio Frio et al. 2011; Foulkes et al. 2011)
		XPO5	Colecteral cancer	Frameshift, insertion	(Melo et al. 2010)
	Cancer/developmental disorder	**SMAD1**, SMAD2, **SMAD3**, **SMAD4**, SMAD5, **SMAD6**, **SMAD7**, SMAD9	Colorectal cancer, Loeys-Dietz syndrome, juvenile polyposis, pancreatic cancer	Missense, nonsense mutation, frameshift	(Schutte et al. 1996; Howe et al. 1998; Broderick et al. 2007; van de Laar et al. 2011; Regalado et al. 2011)
		PRKRA, **TARPBP2**	Colecteral cancer	Frameshift	(Melo et al. 2010)
	Neurological disease	**SNIP1**	Psychomotor retardation, epilepsy, craniofacial dymorphism	Missense mutation	(Puffenberger et al. 2012)
	Pulmonary disease	**SMAD1**, SMAD2, **SMAD3**, **SMAD4**, SMAD5, **SMAD6**, **SMAD7**, **SMAD9**	Pulmonary hypertension, aortic valve disease (AOVD2)	Missense, nonsense mutation	(Nasim et al. 2011; Drake et al. 2011; Tan et al. 2012)
telRNA-binding	Developmental/cardiovascular/pulmonary disease	TERT	Coronary artery disease, dyskeratosis congenita, aplastic anemia	Missense mutation, frameshift	(Yamaguchi et al. 2005; Armanios et al. 2007; Tsakiri et al. 2007; Marrone et al. 2007)
	Developmental disorder	WRAP53	Dyskeratosis congenita	Missense mutation	(Zhong et al. 2011)
7SL–RNA-binding	Hematologic disease	**SRP72**	Bone marrow failure	Missense mutation	(Kirwan et al. 2012)
	Developmental disorder	LARP7, SSB	Alazami syndrome	Base insertion	(Alazami et al. 2012)

al. 1994; Al-Sukhni et al. 2008 Al-Sukhni et al. 2008 Al-Sukhni et al. 2008

RBP class	disease category	RBP family	disease	genetic mutation	reference
immune-stimulatory RNA binder	Autoimmune disease	**IFIH1**, DDX58, DHX58	Aicardi-Goutieres syndrome (AGS)	Missense mutation	(Rice et al. 2014)
	Metabolic disease	**OAS1**, OAS2, OAS3, OASL	Susceptibility to diabetes mellitus	Missense mutation	(Tessier et al. 2006)
	Cancer	**RNASEL**	Prostate cancer	Nonsense, missense mutation	(Carpten et al. 2002; Casey et al. 2002)
RNA/DNA-hybrid binder	Autoimmune/neurological disease	**RNASEH2A**	Aicardi-Goutieres syndrome (AGS)	Missense mutation	(Crow et al. 2006; Rice et al. 2013)
		RNASEH2B	Aicardi-Goutieres syndrome (AGS)	Missense mutation	(Crow et al. 2006)
		RNASEH2C	Aicardi-Goutieres syndrome (AGS)	Missense mutation	(Crow et al. 2006)
		SAMHD1	Aicardi-Goutieres syndrome (AGS), Chilbain lupus 2	Missense mutation	(Rice et al. 2009; Ravenscroft et al. 2011)
		DNMT3A, **DNMT3B**, DNMT3L	Immunodeficiency-centromeric instability-facial anomalies syndrome 1	Missense mutation, deletion	(Xu et al. 1999)
	Neurological disease	**APTX**	Ataxia	Deletion, splice site mutation, missense mutation	(Amouri et al. 2004; Criscuolo et al. 2005)
diverse targets	Neurological disease	**ANG**, RNASE1-4, RNASE6-8	Amyotrophic lateral sclerosis (ALS)	Missense mutation	(Greenway et al. 2006)
		EXOSC3	Pontocerebellar hypoplasia, spinal motor neuron degeneration	Missense mutation, deletion	(Wan et al. 2012)
		RNASET2	Leukoencephalopathy, cancer	Missense mutation, deletion, splice site mutation	(Henneke et al. 2009)
	Developmental disorder	DIS3, DIS3L, **DIS3L2**	Perlman syndrome	Deletion, splice site mutation, missense mutation	(Astuti et al. 2012)
	Metabolic disease/deafness	**PNPT1**	Combined oxidative phosphorylation deficiency	Missense mutation	(Ameln et al. 2012; Vedrenne et al. 2012)
unknown targets	Cardiac disease	**CALR3**, CALR, CANX, CLGN	Cardiomyopathy	Missense mutation	(Chiu et al. 2007)
	Developmental disorder	**ASCC1**	Barrett esophagus	Missense mutation	(Orloff et al. 2011)
	Pulmonary disease	**DNAAF2**	Ciliary dyskinesia	Insertion, nonsense mutation	(Omran et al. 2008)