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The RNA exosome and RNA exosome-linked disease

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ABSTRACT

The RNA exosome is an evolutionarily conserved, ribonuclease complex that is critical for both processing and degradation of a variety of RNAs. Cofactors that associate with the RNA exosome likely dictate substrate specificity for this complex. Recently, mutations in genes encoding both structural subunits of the RNA exosome and its cofactors have been linked to human disease. Mutations in the RNA exosome genes *EXOSC3* and *EXOSC8* cause pontocerebellar hypoplasia type 1b (PCH1b) and type 1c (PCH1c), respectively, which are similar autosomal-recessive, neurodegenerative diseases. Mutations in the RNA exosome gene *EXOSC2* cause a distinct syndrome with various tissue-specific phenotypes including retinitis pigmentosa and mild intellectual disability. Mutations in genes that encode RNA exosome cofactors also cause tissue-specific diseases with complex phenotypes. How mutations in these genes give rise to distinct, tissue-specific diseases is not clear. In this review, we discuss the role of the RNA exosome complex and its cofactors in human disease, consider the amino acid changes that have been implicated in disease, and speculate on the mechanisms by which exosome gene mutations could underlie dysfunction and disease.

Keywords: pontocerebellar hypoplasia type 1b; pontocerebellar hypoplasia type 1c; retinitis pigmentosa; intellectual disability; spinal motor neuropathy; trichohepatoenteric syndrome; RNA exosome; EXOSC2; EXOSC3; EXOSC8; Rrp4; Rrp40; Rrp43; RBM7; SKIV2L; TTC37; Ski2; Ski3; RNA processing/degradation

INTRODUCTION

The RNA exosome is an evolutionarily conserved, ribonuclease complex composed of both structural and catalytic subunits that processes and/or degrades multiple classes of RNAs (Mitchell et al. 1997; Allmang et al. 1999b; Schilders et al. 2005; Liu et al. 2006; Dziembowski et al. 2007; Makino et al. 2013). Recently, mutations in several genes encoding RNA exosome subunits and exosome cofactors have been linked to inherited, tissue-specific diseases. Mutations in the RNA exosome catalytic subunit gene *DIS3* have been linked to cancer, and this topic has recently been covered in several excellent reviews (Flynn et al. 2011; Reis et al. 2013; Chesi and Bergsagel 2015; Robinson et al. 2015). In this review, we focus on mutations in genes encoding RNA exosome structural subunits (*EXOSC2*, *EXOSC3*, and *EXOSC8*) and exosome cofactors (*RBM7*, *SKIV2L*, and *TTC37*) that have been linked to human disease.

Composition/structure of the RNA exosome

First identified in *S. cerevisiae* (Mitchell et al. 1996, 1997; Allmang et al. 1999b), the RNA exosome is composed of 10 conserved core subunits that form a ring-like structure (Fig. 1; Mitchell et al. 1997; Allmang et al. 1999b; Liu et al. 2006; Makino et al. 2013). In humans, the exosome subunits are termed exosome component (EXOSC) proteins. In *S. cerevisiae* and *Drosophila*, most exosome subunits are termed Rrp proteins after the original yeast genetic screen for ribosomal RNA processing (*rrp*) mutants (Mitchell et al. 1996), but a few subunits are named after other yeast genetic screens in which they were identified (Ohkura et al. 1988; Kadowaki et al. 1994; Baker et al. 1998). The 10-subunit core exosome comprises a catalytically inert, central, six-subunit ring (EXOSC4-9; Rrp41/42/43/45/46/Mtr3), a three-subunit cap (EXOSC1-3; Csl4/Rrp4/Rrp40), and a catalytically active ribonuclease (DIS3/Dis3/Rrp44), which associates with the six-subunit ring at the base (Liu et al. 2006; Malet et al. 2010; Makino et al. 2013). In the nucleus, the eukaryotic RNA exosome includes an eleventh riboexonuclease subunit, EXOSC10/Rrp6, which associates with the cap (Makino et al. 2013, 2015; Wasmuth et al. 2014). Notably, EXOSC8/Rrp43 is conserved from yeast to human, but is apparently not present in *Drosophila* (Kiss and Andrulis 2010).

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Article is online at http://www.rnajournal.org/cgi/doi/10.1261/rna.064626.117.

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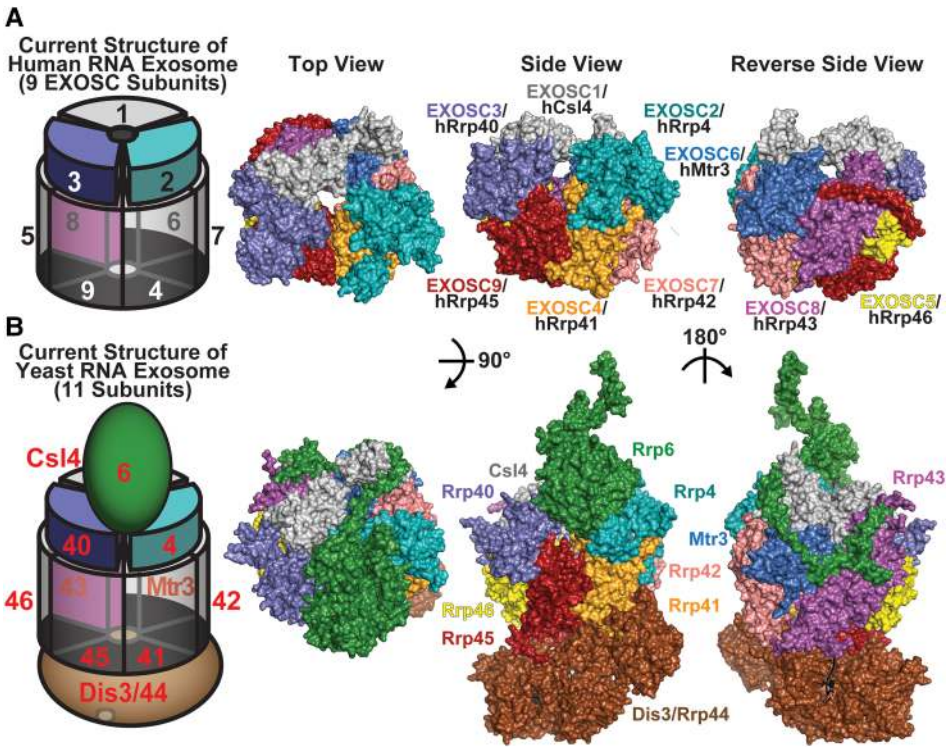

FIGURE 1. Structure of the RNA exosome, a ribonuclease complex that processes/degrades multiple classes of RNA. (*A*) Cartoon representation of the nine-subunit human RNA exosome complex that has been solved thus far (Liu et al. 2006). This nine-subunit core exosome is composed of a three-subunit cap (EXOSC1/2/3) at the *top* and a six-subunit ring (EXOSC4-9) in the *middle*. The active ribonuclease subunit, DIS3, would contact the *bottom* of this structure, but no human structures have been solved to date that include any DIS3 subunit. To the *right* of the cartoon, ribbon representations of this nine-subunit human RNA exosome complex (PDB# 2NN6) (Liu et al. 2006) are shown, depicted in *top*, *side*, and *reverse side* views. The nine-subunit human RNA exosome structure reveals a ring-like architecture composed of three cap subunits—EXOSC1/hCsl4 (gray), EXOSC2/hRrp4 (teal), and EXOSC3/hRrp40 (slate blue) and six PH-like ring subunits—EXOSC4/hRrp41 (orange), EXOSC5/hRrp46 (yellow), EXOSC6/hMtr3 (marine blue), EXOSC7/hRrp42 (salmon red), EXOSC8/hRrp43 (magenta), and EXOSC9/hRrp45 (firebrick red). The EXOSC2/hRrp4 (teal) and EXOSC3/hRrp40 (slate blue) cap subunits altered in novel syndrome and pontocerebellar hypoplasia 1b (PCH1b), respectively (Wan et al. 2012; Di Donato et al. 2016), and EXOSC8 (magenta) ring subunit altered in PCH1c (Boczonadi et al. 2014) are highlighted. (*B*) Cartoon representation of 11-subunit *S. cerevisiae* RNA exosome, which is composed of a three-subunit cap (Csl4/Rrp4/Rrp40) at the *top*, a six-subunit ring (Rrp41/Rrp42/Rrp43/Rrp45/Rrp46/Mtr3), and two catalytic subunits (Dis3/Rrp44 and Rrp6) (Makino et al. 2015). To the *right* of the cartoon, ribbon representations of the structure of this 11-subunit yeast RNA exosome complex (PDB# 5C0W) (Makino et al. 2015) are shown, depicted in *top*, *side*, and *reverse side* views. The 11-subunit yeast RNA exosome structure shows a ring-like shape with three cap subunits—Csl4 (gray), Rrp4 (teal), and Rrp40 (slate blue), six PH-like ring subunits—Rrp41 (orange), Rrp46 (yellow), Mtr3 (marine blue), Rrp42 (salmon red), Rrp43 (magenta), and Rrp45 (firebrick red), and two catalytic subunits—Dis3/Rrp44 (brown) and Rrp6 (forest green). The Rrp6-associated Rrp47 exosome cofactor present in this yeast RNA exosome structure (PDB# 5C0W) (Makino et al. 2015) has been removed. The yeast RNA exosome structure illustrates how the catalytic subunits, Dis3/Rrp44 and Rrp6, interface with the ring-like core of the RNA exosome. The ring-like RNA exosome structures form a central channel through which RNA is directed to the catalytic subunit, Dis3/Rrp44, for processing/degradation. RNA can also gain access to Dis3/Rrp44 in a channel-independent or direct access manner (Liu et al. 2014; Han and van Hoof 2016; Zinder et al. 2016). The color schemes of the human and yeast RNA exosome subunits are identical. Comparison of the human and yeast RNA exosome structures reveals that the RNA exosome structure is highly evolutionarily conserved in eukaryotes.

Structural studies of the RNA exosome complex from archaea (Lorentzen et al. 2007), yeast (Makino et al. 2013, 2015; Wasmuth et al. 2014; Zinder et al. 2016), and humans (Liu et al. 2006) have been invaluable in elucidating exosome function. Figure 1A shows a cartoon and the current structure of the nine-subunit human RNA exosome, which does not include the catalytic subunit, DIS3 (Liu et al. 2006). Figure 1B presents a cartoon and one of the structures of the 11-subunit *S. cerevisiae* RNA exosome, which includes both Dis3/Rrp44 and Rrp6 (Makino et al. 2015).

The structures of the 11-subunit yeast RNA exosome provide important insight into the specific contacts that the catalytic subunits make with the nine-subunit core (Makino et al. 2013, 2015; Wasmuth et al. 2014; Zinder et al. 2016). The structures also reveal how the ring-like complex forms a central channel through which RNA substrates can be threaded from the cap to the hexameric ring to the catalytic subunit, Dis3/Rrp44, at the base for processing/degradation (Liu et al. 2006; Bonneau et al. 2009; Malet et al. 2010; Makino et al. 2013; Wasmuth et al. 2014). Importantly, RNA substrates can also be directly targeted to Rrp6 via the cap (Makino et al. 2015; Zinder et al. 2016) or directly targeted to Dis3/Rrp44 via a channel-independent or direct access mechanism (Liu et al. 2014; Han and van Hoof 2016; Zinder

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et al. 2016). The comparison of the overall architecture of these structures highlights the remarkable evolutionary conservation of the RNA exosome complex. The availability of these elegant RNA exosome structures allows speculation about the function of the specific amino acids in the exosome subunits that are altered in disease.

RNA targets of the RNA exosome

The RNA exosome performs RNA processing/degradation in both the nucleus and the cytoplasm (Butler and Mitchell 2010; Schaeffer et al. 2010; Schneider and Tollervey 2013). The nuclear exosome not only processes numerous noncoding RNAs (ncRNAs), but also degrades many improperly processed, "faulty" RNAs in nuclear surveillance pathways (Houseley et al. 2006; Kilchert et al. 2016). The cytoplasmic exosome functions in general mRNA turnover, but also degrades many improperly processed RNAs in cytoplasmic quality control pathways, including transcripts containing premature termination codons in nonsense-mediated decay (NMD), transcripts lacking termination codons in nonstop decay (NSD), and transcripts with stalls in translation elongation in no-go decay (NGD) (Schaeffer et al. 2010).

RNA targets of the RNA exosome have been identified in yeast (Gudipati et al. 2012; Schneider et al. 2012), flies (Kiss and Andrulis 2010), mice (Flynn et al. 2011; Pefanis et al. 2014), and humans (Preker et al. 2008). One critical function of the RNA exosome is to produce mature, properly processed rRNAs for the ribosome (Mitchell et al. 1996, 1997; Allmang et al. 1999b). Other RNA targets include small ncRNAs that are processed, including snRNAs and snoRNAs (Allmang et al. 1999a; van Hoof et al. 2000a), mature tRNAs that are turned over (Gudipati et al. 2012; Schneider et al. 2012), and unstable ncRNAs that are degraded, including cryptic unstable transcripts (CUTs) (Wyers et al. 2005) in budding yeast and promoter upstream transcripts (PROMPTs) (Preker et al. 2008), upstream antisense RNAs (uaRNAs) (Flynn et al. 2011), and transcription start site-associated RNAs (xTSS-RNAs) (Pefanis et al. 2014) in human cells. Finally, the RNA exosome contributes to quality control by degrading aberrant, improperly processed RNA transcripts, including pre-mRNAs and hypomodified tRNAs (Allmang et al. 2000; Bousquet-Antonelli et al. 2000; Burkard and Butler 2000; Hilleren et al. 2001; Torchet et al. 2002; Kadaba et al. 2004). Thus, the RNA exosome plays critical roles in post-transcriptional processing and turnover of multiple classes of RNA.

RNA exosome cofactors

The specificity of the RNA exosome for target transcripts is thought to be conferred by distinct exosome cofactors that direct the exosome to specific RNAs for processing/degradation (Butler and Mitchell 2010; Schaeffer et al. 2010; Schmidt and Butler 2013; Kilchert et al. 2016; Zinder and Lima 2017). Several evolutionarily conserved exosome cofactors have been identified to date. Nuclear exosome cofactors, including the Trf4/5-Air1/2-Mtr4 polyadenylation (TRAMP)/PAPD5-ZCCHC7-hMTR4/SKIV2L2 complex (LaCava et al. 2005; Vanacova et al. 2005; Wyers et al. 2005; Fasken et al. 2011; Lubas et al. 2011), Mpp6/hMPP6/MPHOS6 (Schilders et al. 2005; Milligan et al. 2008), Rrp47/C1D (Mitchell et al. 2003; Schilders et al. 2007), and the Nrd1-Nab3-Sen1 (NNS) complex/SETX (Vasiljeva and Buratowski 2006; Richard et al. 2013), which play key roles in nuclear RNA processing/degradation, have been identified in both yeast and human cells. The nuclear exosome targeting (NEXT) complex (hMTR4/SKIV2L2-ZCCHC8-RBM7) has also been identified as a key nuclear exosome cofactor in human cells (Lubas et al. 2011). Cytoplasmic exosome cofactors, the Ski complex (Ski2–Ski3–Ski8/SKIV2L-TTC37-WDR61) (Anderson and Parker 1998) and Ski7/HBS1L3 (van Hoof et al. 2000b; Kowalinski et al. 2016), have been identified in yeast and human cells and play important roles in cytoplasmic mRNA degradation (Schaeffer et al. 2010). Notably, the nuclear Mtr4/hMTR4/SKIV2L2 cofactor and cytoplasmic Ski2/SKIV2L cofactor, both DExH box ATP-dependent RNA helicases, play pivotal roles in remodeling RNA substrates for the RNA exosome (Johnson and Jackson 2013; Schneider and Tollervey 2013). Thus far, mutations in genes encoding components of the NEXT complex (*RBM7*) and the Ski complex (*SKIV2L* and *TTC37*) have been linked to human disease (Hartley et al. 2010; Fabre et al. 2012; Giunta et al. 2016).

The RNA exosome genes are essential for life

In *S. cerevisiae*, all RNA exosome genes, with the exception of *RRP6*, are essential (Mitchell et al. 1997; Briggs et al. 1998; Allmang et al. 1999b). In *S. pombe*, a specific study showed that the *dis3* gene is essential (Kinoshita et al. 1991), while genome-wide deletion analysis provides evidence that core exosome components are also essential (Kim et al. 2010). As in *S. cerevisiae*, the nuclear riboexonuclease Rrp6 is not essential in *S. pombe* (Kim et al. 2010). In *Drosophila*, the RNA exosome genes that have been studied (*dDis3, dMtr3, dRrp6, dRrp41, dRrp42*) are essential and critical for normal fly development (Hou et al. 2012; Lim et al. 2013). In mice, only the *Exosc3* gene has been studied and, consistent with the other models analyzed, the gene is essential for viability (Pefanis et al. 2014). These results provide evidence that all core subunits of the RNA exosome are essential for viability, which supports a critical role for the RNA exosome in cells from yeast to mammals.

Mutations in genes encoding RNA exosome subunits cause distinct human diseases

Recently and surprisingly, given that RNA exosome genes are essential, mutations in three genes encoding structural

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subunits of the RNA exosome have been linked to different tissue-specific diseases (Wan et al. 2012; Boczonadi et al. 2014; Di Donato et al. 2016). Specifically, mutations in the structural exosome subunit genes *EXOSC3* and *EXOSC8* have been linked to pontocerebellar hypoplasia (Wan et al. 2012; Rudnik-Schöneborn et al. 2013; Boczonadi et al. 2014; Eggens et al. 2014), and mutations in the structural subunit exosome gene *EXOSC2* have been linked to a novel syndrome that impacts a variety of tissues (Di Donato et al. 2016).

The majority of these mutations are missense mutations that alter conserved amino acids within evolutionarily conserved sequences (Fig. 2). Figure 2A shows the domain structures of the human EXOSC2, EXOSC3, and EXOSC8 proteins as well as the amino acid changes identified in the proteins in individuals with disease. In addition, alignments of human, mouse, *Drosophila*, and *S. cerevisiae* EXOSC2/3/8 ortholog sequences surrounding the altered residues are shown to illustrate the sequence conservation. Table 1 summarizes all the amino acid substitutions in EXOSC2/3/8 that have been identified in affected individuals and describes the corresponding genotypes and phenotypes of the affected individuals. Supplemental Table S1 details all the mutations found in these exosome genes and provides additional clinical information on the affected individuals.

Studies are just beginning to assess the functional consequences of the amino acid substitutions in EXOSC2/3/8. What is perhaps most surprising is that some amino acid substitutions in different RNA exosome subunits impact different tissues altogether. These differential phenotypes suggest that these specific amino acid changes in EXOSC2/3/8, while mild enough to support sufficient exosome activity to allow viability, could have specific consequences that vary in different tissues and/or cell types. Prior to the discovery of these disease-causing mutations, the likely assumption would have been that any impairment of the RNA exosome complex would have similar functional consequences. For these reasons, considering how the disease-linked amino acid substitutions in EXOSC2/3/8 may affect RNA exosome function could provide insights into what specific pathways or processes are altered. Combining the information on the EXOSC2/3/8 variants that has been gleaned from clinical studies, model organisms, and structures of the RNA exosome complex could suggest specific interactions or interfaces that are most likely to be affected by the different amino acid changes. Figure 2 illustrates each of the conserved amino acids in EXOSC2/3/8 that are altered in disease in the context of the human exosome complex structure (Fig. 2B; Liu et al. 2006) and in the isolated EXOSC2/3/8 subunits (Fig. 2C). Taken together, these analyses permit some speculation on the functional consequences of the amino acid changes in EXOSC2/3/8 and suggest some potential models that could explain why amino acid changes in different exosome subunits cause distinct, tissue-specific disease phenotypes.

Exosome subunit gene mutations

EXOSC2

Mutations in *EXOSC2*, which encodes a structural cap subunit of the exosome (Fig. 2B), have been linked to a novel syndrome characterized by early onset retinitis pigmentosa (vision impairment due to degeneration of rod photoreceptor cells in retina), progressive sensorineural hearing loss, hypothyroidism, premature aging, and mild intellectual disability (Di Donato et al. 2016). The EXOSC2 protein cap subunit contains three domains: an N-terminal domain, a putative RNA-binding S1 domain, and a putative RNA-binding K homology (KH) domain (Fig. 2A). Exome sequencing of three affected individuals from two unrelated families revealed that two individuals from one family have homozygous *EXOSC2* (G30V) mutations in the N-terminal domain of EXOSC2, while one individual from the second family harbors compound heterozygous *EXOSC2* (G30V) and *EXOSC2* (G198D) mutations in the N-terminal and KH domain, respectively, of EXOSC2 (Fig. 2A,C). All three affected individuals showed relatively mild disease (alive at ages 6, 44, and 28) and borderline or mild cerebellar atrophy.

Analysis of the human RNA exosome structure suggests that the highly conserved G30 residue in EXOSC2/Rrp4 could be important for intersubunit interactions with EXOSC4/Rrp41 (Fig. 2B; Liu et al. 2006). Structural modeling suggests the EXOSC2-G30V substitution could impair interactions with key EXOSC4 residues (D153, D154, F155) (Di Donato et al. 2016). In contrast, the conserved G198 residue in EXOSC2/Rrp4, which is located at the end of a β-strand in the KH domain, could play a more structural role within EXOSC2/Rrp4 (Fig. 2C). Structural modeling suggests the EXOSC2-G198D substitution could shorten and disturb the β-hairpin structure in EXOSC2 (Di Donato et al. 2016). At present, little functional analysis of the EXOSC2/Rrp4 variants has been performed.

EXOSC3

Mutations in *EXOSC3*, which like *EXOSC2* encodes a structural cap subunit of the RNA exosome (Fig. 2B), have been linked to pontocerebellar hypoplasia type 1b (PCH1b), an autosomal-recessive, neurodegenerative disease characterized by significant atrophy of the pons and cerebellum, Purkinje cell abnormalities, and degeneration of spinal motor neurons, starting at birth (MIM#606489) (Wan et al. 2012; Rudnik-Schöneborn et al. 2013; Eggens et al. 2014). The cerebellum and pons integrate information from sensory systems, the spinal cord, and other parts of the brain to regulate motor movements, breathing, and learning motor behavior (Apps and Garwicz 2005). Individuals with PCH1b also show muscle atrophy/weakness, microcephaly (smaller head than normal), developmental delay, and brainstem involvement (Wan et al. 2012; Rudnik-Schöneborn et al. 2013; Eggens et al. 2014). Most individuals with

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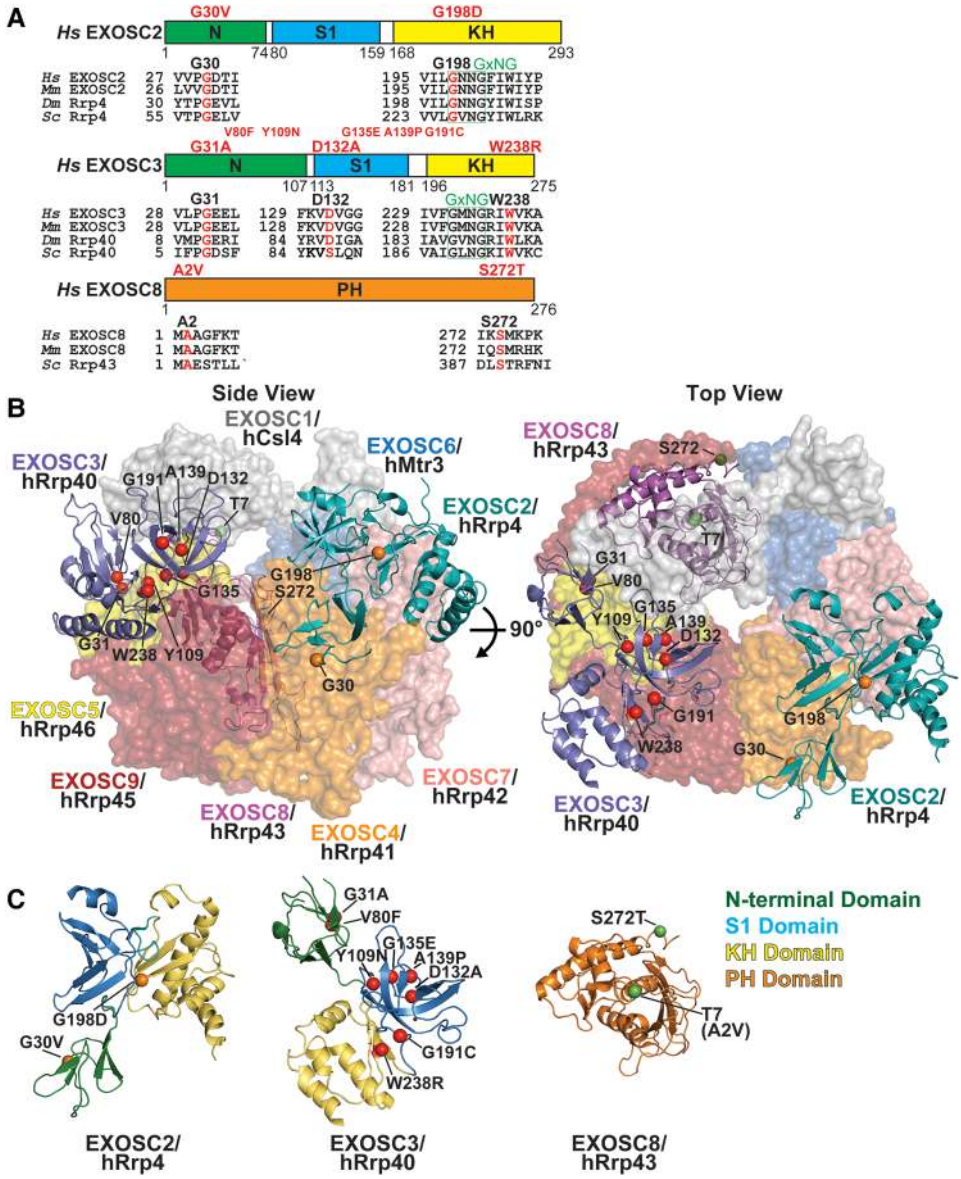

FIGURE 2. Amino acid substitutions identified in the EXOSC2, EXOSC3, and EXOSC8 subunits of the RNA exosome in individuals with pontocerebellar hypoplasia and novel syndrome. (*A*) Domain structures of human EXOSC2, EXOSC3, and EXOSC8 proteins highlighting the amino acid changes identified in affected individuals (Wan et al. 2012; Rudnik-Schöneborn et al. 2013; Zanni et al. 2013; Boczonadi et al. 2014; Eggens et al. 2014; Halevy et al. 2014; Di Donato et al. 2016). Amino acid changes in the EXOSC2 and EXOSC3 cap subunits (shown in red), linked to a novel syndrome and pontocerebellar hypoplasia type 1b (PCH1b), respectively, are located in the N-terminal domain (green), the central putative RNA-binding S1 domain (blue), or the C-terminal putative RNA-binding K homology (KH) domain (yellow). Amino acid changes in the EXOSC8 ring subunit (shown in red), linked to pontocerebellar hypoplasia type 1c (PCH1c), are located in the PH-like domain (orange). *Below* the domain structures, alignments of EXOSC2/3/8 ortholog sequences from human (*Hs*), mouse (*Mm*), *Drosophila melanogaster* (*Dm*), and *S. cerevisiae* (*Sc*) that surround the evolutionarily conserved residues altered in disease (highlighted in red, labeled in black *above*) are shown. The GxNG motif (boxed in green) present in the EXOSC2/Rrp4 and EXOSC3/Rrp40 KH domains may play a structural role, as the GXNG motif in *Sc*Rrp40 is buried at the interface between the S1 and KH domains (Oddone et al. 2007). Amino acid positions are shown *below* the domain structures. (*B*) Structures of the EXOSC2, EXOSC3, and EXOSC8 subunits in the context of the structure of the human RNA exosome complex that highlight the conserved residues altered in disease. The nine-subunit human exosome structure (PDB# 2NN6) (Liu et al. 2006), depicted in *top* and *side* views, shows ribbon representations of the EXOSC2/hRrp4 (teal), EXOSC3/hRrp40 (slate blue), and EXOSC8/hRrp43 (magenta) subunits and highlights the conserved residues altered in disease (colored spheres): EXOSC2—G30 and G198 (orange spheres), EXOSC3—G31, V80, Y109, D132, G135, A139, G191, and W238 (red spheres), and EXOSC8—S272 (green sphere), which are labeled in black. The EXOSC8 amino acid T7 (green sphere) is labeled to show the approximate position of the conserved amino acid A2 that is altered in PCH1c individuals, but could not be labeled because it was not resolved in the structure. Transparent, surface representations of the EXOSC1/hCsl4 (gray), EXOSC4/hRrp41 (orange), EXOSC5/hRrp46 (yellow), EXOSC6/hMtr3 (marine blue), EXOSC7/hRrp42 (salmon red), and EXOSC9/hRrp45 (firebrick red) subunits are depicted. (*C*) Separate ribbon representations of the EXOSC2/hRrp4, EXOSC3/hRrp40, and EXOSC8/hRrp43 subunits that highlight the domains of the proteins and the amino acid substitutions identified in disease. The EXOSC2-G30V and -G198D amino acid substitutions are located in the N-terminal domain (green) and putative RNA-binding KH domain (yellow), respectively. The EXOSC3-G31A and -V80F substitutions are located in the N-terminal domain (green), the EXOSC3-Y109N, -D132A, -G135E, -A139P, and -G191C substitutions are located in the putative RNA-binding S1 domain (blue), and the EXOSC3-W238R substitution is located in the KH domain (yellow). The EXOSC8-S272T substitution is located at the C-terminal end of the PH-like domain (orange). The EXOSC8-T7 residue is labeled to show the approximate position of the EXOSC8-A2V substitution at the N-terminal end of the PH-like domain (orange), as the A2 residue could not be resolved in the structure.

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TABLE 1. Exosome subunit/cofactor variants linked to disease

Exosome subunit/cofactor	Amino acid substitution	Genotype of affected individuals		Phenotype of affected individuals	Disease severity
EXOSC2	G30V	G30V	Homozygous	Novel syndrome[a]	Mild
EXOSC2	G198D	G198/G30V	Heterozygous	Novel syndrome[a]	Mild
EXOSC3	G31A	G31A	Homozygous	PCH1b[b]	Severe
EXOSC3	Y80F	V80F/D132A	Heterozygous	PCH1b,[b] SP[c]	Mild
EXOSC3	Y109N	Y109N/D132A	Heterozygous	PCH1b[b]	Severe
EXOSC3	D132A	D132A	Homozygous	PCH1b[b]	Mild
		D132A/Null[e]	Heterozygous	PCH1b[b]	Severe
EXOSC3	G135E	G135E	Homozygous	PCH1b[b]	Severe
EXOSC3	A139P	A139P/D132A	Heterozygous	PCH1b[b]	Severe
EXOSC3	G191C	G191C	Homozygous	PCH1b,[b] SP[c]	Mild
EXOSC3	W238R	W238R/G31A	Heterozygous	PCH1b[b]	Severe
EXOSC8	A2V	A2V	Homozygous	PCH1c[d]	Mild
EXOSC8	S272T	S272T	Homozygous	PCH1c[d]	Severe
RBM7	P79R	P79R	Homozygous	SMA-like[f]	Severe
SKIV2L	V341G	V341G/Null[e]	Heterozygous	SD/THES2[g]	Mild
SKIV2L	G631S	G631S/Null[e]	Heterozygous	SD/THES2[g]	Mild
TTC37	G673D	G673D/Null[e]	Heterozygous	SD/THES1[g]	Mild
TTC37	L761P	L761P	Homozygous	SD/THES1[g]	Mild
TTC37	A1077D	A1077D	ND[h]	SD/THES1[g]	Mild
TTC37	P1270A	P1270A	Homozygous	SD/THES1[g]	Mild
TTC37	D1283N	D1283N	ND[h]	SD/THES1[g]	Mild
TTC37	L1485R	L1485R/Null[e]	Heterozygous	SD/THES1[g]	Mild
TTC37	R1503C	R1503C	Homozygous	SD/THES1[g]	Severe
TTC37	L1505S	L1505S/Null[e]	Heterozygous	SD/THES1[g]	Mild

Summary of all amino acid substitutions identified to date in EXOSC2, EXOSC3, and EXOSC8 exosome subunits and RBM7, SKIV2L, and TTC37 exosome cofactors in individuals with disease and the associated genotypes, phenotypes, and severity of disease of the affected individuals. At present, *EXOSC2* mutations have been identified in individuals with a novel syndrome (Di Donato et al. 2016), *EXOSC3* mutations have been identified in individuals with pontocerebellar hypoplasia type 1b (PCH1b) (Wan et al. 2012; Rudnik-Schöneborn et al. 2013; Zanni et al. 2013; Eggens et al. 2014; Halevy et al. 2014), and *EXOSC8* mutations have been identified in individuals with pontocerebellar hypoplasia type 1c (PCH1c) (Boczonadi et al. 2014). In addition, an *RBM7* mutation has been identified in an individual with spinal motor neuropathy, similar to spinal muscular atrophy (Giunta et al. 2016), and *SKIV2L* and *TTC37* mutations have been identified in individuals with trichohepatoenteric syndrome (THES) (Hartley et al. 2010; Fabre et al. 2011, 2012; Kammermeier et al. 2014; Oz-Levi et al. 2015; Lee et al. 2016b; Zheng et al. 2016; Kinnear et al. 2017). Although most affected individuals with exosome subunit/cofactor mutations have reduced life span and quality of life, mild disease here specifically indicates that the individuals are still living or lived for several years, whereas severe disease indicates that the individuals died within two years. Further details on these missense mutations and other mutations in the exosome subunit/cofactor genes, as well as number of affected individuals, life span of individuals, and specific references for each mutation are presented in Supplemental Table S1 (RNA exosome subunits) and Supplemental Table S2 (exosome cofactors).
[a]Retinitis pigmentosa, hearing loss, premature aging, short stature, mild intellectual disability.
[b]Pontocerebellar hypoplasia type 1b.
[c]Spastic paraplegia.
[d]Pontocerebellar hypoplasia type 1c.
[e]Frameshift, premature termination codon, indel.
[f]Spinal motor neuropathy that is spinal muscular atrophy-like.
[g]Syndromic diarrhea/trichohepatoenteric syndrome.
[h]Not determined—only one mutation in *TTC37* identified to date.

PCH1b do not live past childhood and current treatment is purely palliative. Like EXOSC2, the EXOSC3 cap subunit contains three domains: an N-terminal domain, a putative RNA-binding S1 domain, and a putative RNA-binding KH domain (Fig. 2A).

Exome sequencing of individuals with PCH1b from thirty-eight unrelated families has identified several different *EXOSC3* mutations (Table 1; Fig. 2; Supplemental Table S1; Wan et al. 2012; Biancheri et al. 2013; Rudnik-Schöneborn et al. 2013; Schwabova et al. 2013; Eggens et al. 2014; Di Giovambattista et al. 2017; Schottmann et al. 2017). In particular, 13 individuals with severe PCH1b (life span ≤2 yr) carried homozygous *EXOSC3* (G31A) mutations in the N-terminal domain of EXOSC3, and 18 individuals with PCH1b that exhibited a less severe disease (life span ≥3 yr) had homozygous *EXOSC3* (D132A) mutations in the S1 domain of EXOSC3. In addition, 14 individuals with severe PCH1b (life span ≤2 yr) possessed compound heterozygous *EXOSC3* (D132A) and *EXOSC3* (Null allele [frameshift; premature termination codon; indel], Y109N, or A139P) mutations. Finally, two individuals with PCH1b contained compound heterozygous *EXOSC3* (G31A) and *EXOSC3* (W238R) mutations in the N-terminal domain and KH domain, respectively, of EXOSC3; one individual

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with PCH1b had homozygous *EXOSC3* (G135E) mutations in the S1 domain of EXOSC3, and all exhibited severe disease.

EXOSC3 mutations that cause a mild, clinically diverse form of PCH1b with additional phenotypes (Zanni et al. 2013; Halevy et al. 2014) have also been identified in six individuals. In one family, two affected individuals have compound heterozygous *EXOSC3* (V80F) and *EXOSC3* (D132A) mutations and exhibit intellectual disability, spastic paraplegia [spasticity (stiffness) and contraction in lower limbs], and cerebellar atrophy, but no microcephaly and a normal brainstem (Zanni et al. 2013). In a second family, four affected individuals harbor homozygous *EXOSC3* (G191C) mutations and show spastic paraplegia and mild cerebellar atrophy, but no microcephaly and normal pons (Halevy et al. 2014). Thus, distinct amino acid changes in EXOSC3 can cause different functional consequences and disease phenotypes, even impacting different regions of the brain.

Analysis of the human RNA exosome structure suggests that the evolutionarily conserved G31, D132, and W238 residues in EXOSC3/Rrp40, located in the N-terminal, S1 and KH domain, respectively, may be important for intersubunit interactions with EXOSC5/Rrp46 and EXOSC9/Rrp45 (Fig. 2; Liu et al. 2006). In particular, the G31 residue in EXOSC3 is tightly packed against the surface of EXOSC5 and, therefore, the EXOSC3-G31A substitution could impair the interaction with EXOSC5 (Fig. 2B; Fasken et al. 2017). The D132 residue in EXOSC3 is located in a loop between strands in the S1 domain and, therefore, the EXOSC3-D132A substitution could impair the folding of the loop and subsequently disturb interactions with EXOSC5 and EXOSC9 (Fig. 2B,C; Fasken et al. 2017). The W238 residue in EXOSC3, which lies in a pocket between the S1 and KH domains, could position residues in EXOSC3 to interact with EXOSC9 and, therefore, the EXOSC3-W238R substitution could weaken interactions between EXOSC3 and EXOSC9 (Fig. 2B,C; Fasken et al. 2017). These analyses suggest that PCH1b-associated substitutions in EXOSC3 could impair interactions with other exosome subunits, leading to compromised RNA exosome function and disease.

Some recent studies have used model organisms to assess the function of the EXOSC3/Rrp40 variants identified in humans with PCH1b. The stability of the budding yeast rrp40-W195R variant, corresponding to the human EXOSC3-W238R variant, is reduced compared to wild-type Rrp40 (Fasken et al. 2017). In addition, the expression levels of the mouse EXOSC3-G31A and EXOSC3-W237R variants, corresponding to human EXOSC3-G31A and -W238R, in a mouse neuronal cell line are reduced compared to wild-type mouse EXOSC3 (Fasken et al. 2017). These data could suggest that the EXOSC3 substitutions impair the folding of the EXOSC3 protein. Budding yeast cells that express the rrp40-W195R variant as the sole Rrp40 protein show impaired processing of rRNA and degradation of ncRNAs such as CUTs (Fasken et al. 2017; Gillespie et al. 2017). In zebrafish, morpholino knockdown of *exosc3* in embryos shrinks the hindbrain. Expression of wild-type zebrafish *exosc3* mRNA rescues this hindbrain development defect, but mutant zebrafish *exosc3* mRNA corresponding to *EXOSC3* (G31A, D132A, or W238R) fail to rescue this hindbrain defect (Wan et al. 2012). Notably, knockdown of *exosc3* most severely affects brachimotor facial neurons and disrupts the structure of the Purkinje cell layer/cerebellum (Giunta et al. 2016). These results support the notion that the amino acid substitutions in EXOSC3 identified in individuals with PCH1b impair the function of the RNA exosome.

EXOSC8

Mutations in *EXOSC8*, encoding a hexameric ring subunit of the RNA exosome (Fig. 2B), have been linked to pontocerebellar hypoplasia type 1c (PCH1c), an autosomal-recessive, neurodegenerative disorder characterized by psychomotor deficit, cerebellar and corpus callosum hypoplasia, hypomyelination, and spinal muscular atrophy (SMA) starting at birth (MIM#606019) (Boczonadi et al. 2014). Individuals who suffer from PCH1c also show severe muscle weakness, impaired vision and hearing, and often die due to respiratory failure (Boczonadi et al. 2014). Like PCH1b-affected individuals with *EXOSC3* mutations, PCH1c-affected individuals with *EXOSC8* mutations primarily exhibit defects in spinal motor neurons and Purkinje cells; however, PCH1c-affected individuals also show defects in oligodendroglia that lead to hypomyelination (Boczonadi et al. 2014). The EXOSC8 subunit contains a catalytically inert, PH-like ribonuclease domain (Fig. 2A).

Exome sequencing of 10 individuals with severe PCH1c (life span $\leq$2 yr), eight from one family and two from a second family, revealed that all 10 affected individuals carried homozygous *EXOSC8* (S272T) mutations (Table 1; Fig. 2A; Supplemental Table S1). In addition, two individuals from a third family that showed a less severe disease (life span $\geq$2.3 yr) harbored homozygous *EXOSC8* (A2V) mutations (Table 1; Fig. 2A; Supplemental Table S1). Examination of the human RNA exosome structure suggests that the conserved S272 residue in EXOSC8/Rrp43, located in the PH domain, could be important for interactions with EXOSC9/Rrp45 and/or impact the central channel opening at the bottom of the RNA exosome complex where single-stranded RNA is funneled (Fig. 2B,C; Liu et al. 2006). The position of the T7 residue at the N terminus of EXOSC8, which is the first residue of EXOSC8 visible in this human RNA exosome structure (Liu et al. 2006), suggests the conserved A2 residue in EXOSC8/Rrp43 could potentially interact with EXOSC1/Csl4 or impact an opening at the side of the RNA exosome (Fig. 2B,C).

Analysis of the EXOSC8/Rrp43 variants in cells of PCH1c-affected individuals shows that the expression levels of the EXOSC8 protein variants are severely reduced compared to healthy controls. In particular, EXOSC8-S272T variant levels

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are reduced in myoblasts of affected individuals, and EXOSC8-A2V variant levels are decreased in fibroblasts of affected individuals (Boczonadi et al. 2014). Importantly, in EXOSC8-S272T-expressing myoblasts of affected individuals, the level of EXOSC3 is also severely reduced, suggesting that depletion of EXOSC8 leads to a reduction of other exosome subunits and potentially depletes the entire RNA exosome complex (Boczonadi et al. 2014). PCH1c-affected individuals with EXOSC8-S272T variants also have muscle with variable myofiber size, moderately decreased function of mitochondrial respiratory chain complexes, and brain and spinal cord with profound loss of myelin. Notably, EXOSC8-A2V-expressing fibroblasts of affected individuals show increased levels of developmental *HOX* mRNAs and the *HOTAIR* long ncRNA, a key epigenetic regulator of gene expression (Giunta et al. 2016). In addition, EXOSC8-S272T-expressing myoblasts of affected individuals show elevated levels of some myelin-related, AU-rich element (ARE)-containing mRNAs (e.g., *MBP*, *MOBP*); ARE mRNAs have previously been shown to be targets of the RNA exosome (Mukherjee et al. 2002; Boczonadi et al. 2014). These data suggest that the reduced EXOSC8 variant levels in PCH1c-affected individuals can impair RNA exosome function, leading to accumulation of *HOX* and myelin-related mRNAs and potential disruption of development and myelin synthesis. In support of a role for EXOSC8 in the brain, morpholino knockdown of *exosc8* in zebrafish embryos disrupts normal hindbrain development, altering the structures of the Purkinje cell layer/cerebellum and neuromuscular junction and impairing growth of motor neuron axons (Boczonadi et al. 2014; Giunta et al. 2016).

Mutations in genes encoding RNA exosome cofactors cause distinct human diseases

In addition to mutations in genes encoding structural RNA exosome subunits, mutations in three genes encoding exosome cofactors have been linked to different tissue-specific diseases (Hartley et al. 2010; Fabre et al. 2012; Giunta et al. 2016). In particular, a mutation in the exosome cofactor gene *RBM7* has been linked to spinal motor neuropathy (Giunta et al. 2016), and mutations in the exosome cofactor genes *SKIV2L* and *TTC37* have been linked to syndromic diarrhea/trichohepatoenteric syndrome (Hartley et al. 2010; Fabre et al. 2011, 2012).

The *RBM7* mutation is a missense mutation, but the majority of *SKIV2L* and *TTC37* mutations that have been identified to date are nonsense mutations predicted to cause loss of function. However, a few *SKIV2L* and *TTC37* missense mutations have been identified (Fig. 3). Figure 3A and 3C show the domain structures of the human RBM7, SKIV2L, and TTC37 proteins as well as the amino acid changes identified in the proteins in individuals with disease. Table 1 summarizes all the amino acid substitutions in RBM7, SKIV2L, and TTC37 that have been identified in affected individuals as well as the corresponding genotypes and phenotypes. Supplemental Table S2 details all the mutations found in these exosome cofactor genes and provides additional clinical information on the affected individuals.

Exosome cofactor gene mutations

RBM7

A mutation in *RBM7*, encoding a component of the nuclear exosome cofactor, the NEXT complex, has been linked to a spinal motor neuropathy, similar to spinal muscular atrophy (Giunta et al. 2016). The affected individual exhibited defects in spinal motor neurons, hypotonia (decreased muscle tone), muscle weakness/atrophy, and respiratory difficulties, and passed away due to respiratory failure (Giunta et al. 2016). The affected individual's brain was normal with no cognitive difficulties (Giunta et al. 2016). The RNA-binding protein RBM7, the Zn-knuckle protein ZCCHC8, and the RNA helicase hMTR4/SKIV2L2 form the nuclear exosome targeting (NEXT) complex, which recruits the RNA exosome to ncRNAs and mRNAs for their degradation/processing in the nucleus (Lubas et al. 2011). RBM7 contains a single, N-terminal RNA recognition motif (RRM) that recognizes U-rich pyrimidine sequences (Hrossova et al. 2015). Although the targets directly regulated by RBM7 have not yet been fully defined, a number of RNAs that associate with RBM7 in HeLa cells have been identified, including short-lived ncRNAs (e.g., PROMPTs), 3′-extended sn(o) RNAs, and intron-containing pre-mRNAs (Fig. 3A,B; Hrossova et al. 2015; Lubas et al. 2015). In addition, the RBM7 RRM contains a proline-rich region that not only directly interacts with ZCCHC8 (Fig. 3B), but also, in a mutually exclusive manner, binds to SAP145, a spliceosomal SF3b complex component, providing a potential mechanism for how the NEXT complex recognizes intronic RNAs (Falk et al. 2016).

Exome sequencing of the affected individual with severe disease (life span = 24 mo) revealed a homozygous *RBM7* (P79R) mutation in the RBM7 RRM (Table 1; Fig. 3A,B; Supplemental Table S2; Giunta et al. 2016). Analysis of the recent crystal structure of the human RBM7-ZCCHC8 core complex shows that the RBM7 RRM has a typical RRM fold (β1–α1–β2–β3–α2–β4), with an additional β-strand ($\beta4^{add}$) in the α2–β4 loop and a hydrophobic pocket between α1 and $\beta4^{add}$ with key residues (L25, L29, I73, L75, Y76) that interact with the ZCCHC8 αA helix (Fig. 3B; Falk et al. 2016). Critically, the P79 residue in the RBM7 RRM is located at the start of the β4-strand, close to the $\beta4^{add}$-strand that contacts ZCCHC8, suggesting the RBM7-P79R substitution could impact the conformation of the $\beta4^{add}$-strand and potentially disrupt the RBM7-ZCCHC8 interaction and the integrity of the NEXT complex. As RBM7 β4-strand residues (e.g., K81) are important for binding pyrimidines in RNA (Hrossova et al. 2015), the RBM7-P79R substitution could

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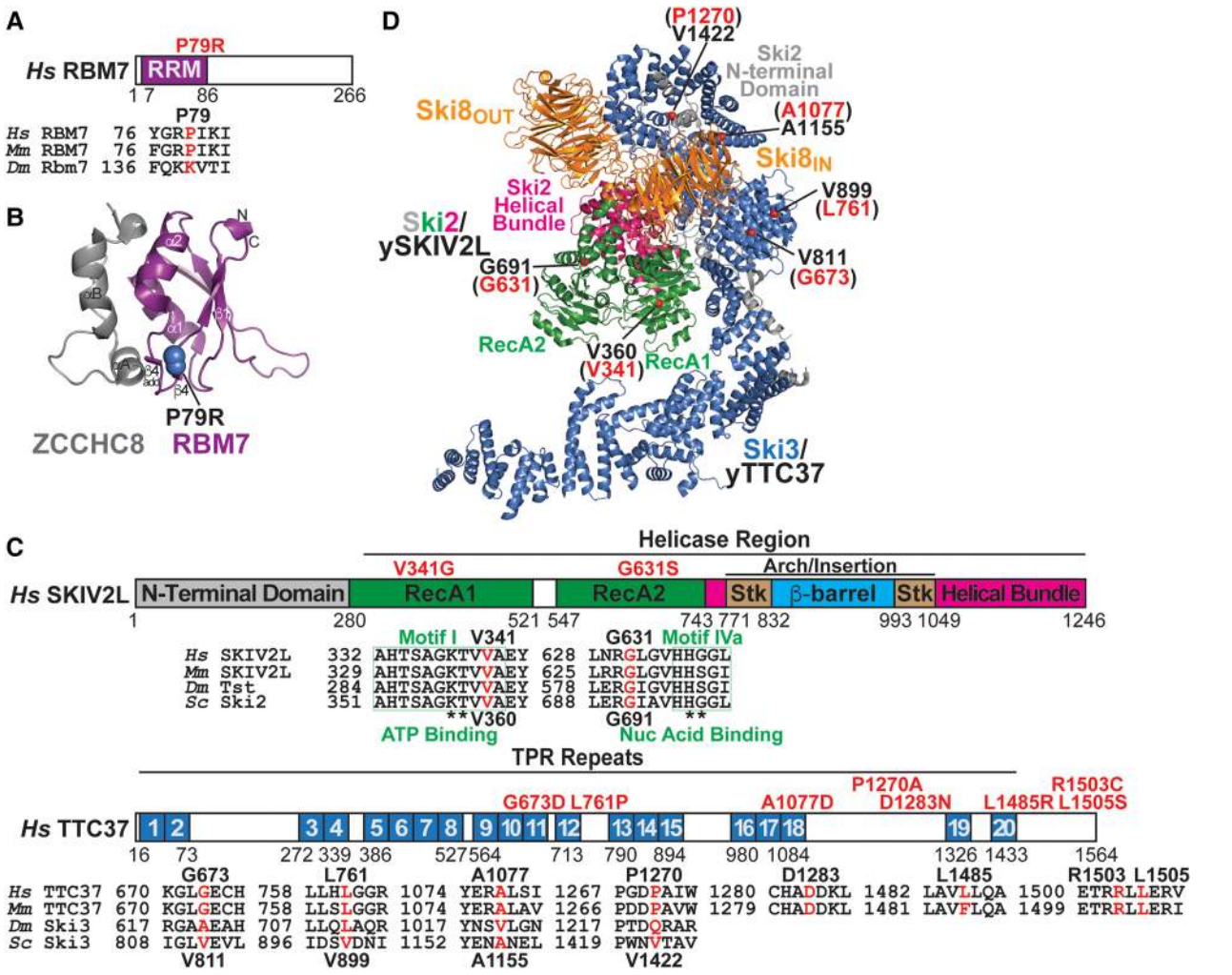

FIGURE 3. Amino acid substitutions identified in RBM7 of the nuclear exosome cofactor, the NEXT complex, and SKIV2L and TTC37 of the cytoplasmic exosome cofactor, the Ski complex, in individuals with spinal motor neuropathy and syndromic diarrhea/trichohepatoenteric syndrome, respectively. (*A*) Domain structure of human RBM7 protein highlighting the P79R amino acid change identified in an individual with spinal motor neuropathy (Giunta et al. 2016). The P79R amino acid change in RBM7 (shown in red) is located in the N-terminal RNA recognition motif (RRM) domain (purple). *Below* the domain structure, alignments of RBM7 ortholog sequences from human (*Hs*), mouse (*Mm*), and *Drosophila melanogaster* (*Dm*) that surround the evolutionarily conserved residue altered in disease (highlighted in red) are shown. (*B*) Structure of the RBM7-ZCCHC8 core of the NEXT complex that highlights the conserved P79 residue in RBM7. A ribbon representation of the human RBM7-ZCCHC8 structure (PDB# 5LXR) (Falk et al. 2016) shows the RBM7 RRM (purple) and ZCCHC8 proline-rich region (gray) and highlights the conserved P79 residue altered in disease (dark blue sphere). (*C*) Domain structures of human SKIV2L and TTC37 proteins highlighting the amino acid changes identified in individuals with trichohepatoenteric syndrome (Hartley et al. 2010; Fabre et al. 2011, 2012; Kammermeier et al. 2014; Oz-Levi et al. 2015; Lee et al. 2016b; Zheng et al. 2016; Kinnear et al. 2017). Amino acid changes in SKIV2L (shown in red), linked to disease, are located in the RecA1 and RecA2 domains (green) in the helicase region. SKIV2L has an N-terminal domain (gray) and C-terminal helicase region, containing two RecA domains (green), a helical bundle domain (pink), and an arch/insertion domain composed of stalk (Stk) regions (brown) and a β-barrel region (light blue). The SKIV2L domain organization is based on sequence alignment with *S. cerevisiae* Ski2 (Halbach et al. 2012). Amino acid changes in TTC37 (shown in red), linked to disease, are located within and between tetratricopeptide repeat (TPR) motifs (marine blue). TTC37 contains 20 predicted TPR motifs. *Below* the domain structures, alignments of SKIV2L and TTC37 ortholog sequences from human (*Hs*), mouse (*Mm*), *Drosophila melanogaster* (*Dm*), and *S. cerevisiae* (*Sc*) that surround the evolutionarily conserved residues altered in disease (highlighted in red) are shown. Human SKIV2L and TTC37 residues altered in disease (labeled in black *above*) and corresponding conserved *S. cerevisiae* Ski2 and Ski3 residues (labeled in black *below*) are shown. In SKIV2L, conserved Motif I in RecA1 and Motif IVa in RecA2 (boxed in green) that bind to ATP and nucleic acid, respectively, in other helicases are shown, with specific residues that contact ATP and nucleic acid marked by asterisks (Fairman-Williams et al. 2010; Jankowsky 2011; Johnson and Jackson 2013). (*D*) Structure of the *S. cerevisiae* Ski complex, composed of Ski2, Ski3, and two Ski8 proteins, that highlights the positions of conserved residues in yeast Ski2/ySKIV2L and Ski3/yTTC37 altered in SKIV2L and TTC37 in individuals with disease. A ribbon representation of the Ski complex structure (PDB# 4BUJ) (Halbach et al. 2013), depicted in side view, shows Ski2/ySKIV2L (gray; green; pink), Ski3/yTTC37 (marine blue), and two Ski8 proteins $Ski8_{OUT}$ and $Ski8_{IN}$ (located in *outer* and *inner* positions in complex) (orange) and highlights the conserved residues altered in disease (red spheres). The human SKIV2L residues—V341 and G631—and TTC37 residues—G673, L761, A1077, and P1270—altered in disease are labeled in red in parentheses and the corresponding, conserved yeast Ski2 residues—V360 and G691—and Ski3 residues—V811, V899, A1155, and V1422 are labeled in black. The Ski2 N-terminal domain (gray), RecA1 and RecA2 domains (green), with Motif I and Motif IVa (yellow), and helicase bundle domain (pink) are depicted.

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also disturb the β4-strand conformation and impair RNA binding.

Analysis of the expression of the RBM7-P79R variant in fibroblasts from the affected individual reveals that the level of the RBM7-P79R variant is greatly reduced (by 63%) compared to healthy controls (Giunta et al. 2016), suggesting the P79R substitution impairs the folding/stability of RBM7. Interestingly, the level of wild-type RBM7 is reduced in fibroblasts from a PCH1c-affected individual with a low level of the EXOSC8-A2V variant (Boczonadi et al. 2014), suggesting reduced EXOSC8/RNA exosome stability leads to decreased RBM7/NEXT complex stability. Like EXOSC8-A2V-expressing fibroblasts, RBM7-P79R-expressing fibroblasts also show elevated levels of *HOX* mRNAs and the *HOTAIR* ncRNA (Giunta et al. 2016), suggesting that RNA degradation by the NEXT/RNA exosome complex is impaired. Future studies will be required to reconcile the putative RBM7 targets identified in cultured cells (Hrossova et al. 2015; Lubas et al. 2015) with those RNA targets impacted in affected individuals. Importantly, knockdown of *rbm7* in zebrafish embryos alters hindbrain structure, particularly vagal brachimotor neurons and, to a mild extent, the Purkinje cell layer/cerebellum, supporting a role for RBM7 in the brain (Giunta et al. 2016).

SKIV2L

Mutations in *SKIV2L*, encoding a component of the cytoplasmic exosome cofactor, the Ski complex, have been linked to syndromic diarrhea/trichohepatoenteric syndrome (SD/THES2), an autosomal-recessive disease characterized by intractable diarrhea, facial dysmorphism, intrauterine growth retardation, immunodeficiency, and hair abnormalities (woolly hair) (MIM#614602) (Fabre et al. 2012). The human SKIV2L (superkiller viralicidic activity 2-like) protein is a DEVH box ATPase and putative RNA helicase and is the ortholog of budding yeast ATPase/RNA helicase Ski2 (Dangel et al. 1995; Lee et al. 1995). Yeast Ski2, Ski3, and Ski8 form the Ski (Superkiller) complex, a cytoplasmic exosome cofactor that is required for cytoplasmic 3′-5′ mRNA turnover (Anderson and Parker 1998; Brown et al. 2000), nonstop decay (van Hoof et al. 2002), and nonsense-mediated decay (Mitchell and Tollervey 2003). SKIV2L has a unique N-terminal domain and a C-terminal helicase region (Fig. 3C).

Exome sequencing of 19 individuals with SD/THES2 from 16 unrelated families revealed several different mutations in *SKIV2L* (Table 1; Fig. 3C; Supplemental Table S2; Fabre et al. 2012, 2013; Morgan et al. 2013; Kammermeier et al. 2014; Monies et al. 2015; Ashton et al. 2016; Lee et al. 2016b; Zheng et al. 2016; Bick et al. 2017). The majority of *SKIV2L* mutations in affected individuals are premature termination codons, frameshift mutations, deletions, or splice site mutations predicted to cause loss of SKIV2L function (Supplemental Table S2). However, two missense mutations in *SKIV2L* were identified in four affected individuals. One affected individual harbors compound heterozygous *SKIV2L* (V341G) and *SKIV2L* (W283X) mutations in the RecA1 helicase domain of SKIV2L, while three affected individuals possess compound heterozygous *SKIV2L* (G631S) and *SKIV2L* (premature termination codon [R374X or R1063X]) mutations in the RecA2 helicase domain and RecA1 or helical bundle domain of SKIV2L, respectively (Table 1; Fig. 3C; Supplemental Table S2).

The location of the conserved V341 and G631 residues altered in disease in the SKIV2L helicase region suggests that substitutions of these residues could impair SKIV2L function by altering ATP and RNA binding. In particular, the SKIV2L-V341 residue, corresponding to yeast Ski2-V360, is located in Motif I in the RecA1 helicase domain, which binds to ATP in other helicases (Fairman-Williams et al. 2010; Jankowsky 2011; Johnson and Jackson 2013), suggesting the SKIV2L-V341G substitution could alter ATP binding and/or ATPase function of SKIV2L (Fig. 3C,D). The SKIV2L-G631 residue, however, corresponding to yeast Ski2-G691, is located near Motif IVa in the RecA2 helicase domain, which binds to nucleic acid in other helicases (Fairman-Williams et al. 2010; Jankowsky 2011; Johnson and Jackson 2013), suggesting the SKIV2L-G631S substitution could alter RNA binding (Fig. 3C,D). At this juncture, no functional studies of SKIV2L/Ski2 variants linked to SD/THES2 have been performed.

TTC37

Mutations in *TTC37*, encoding a second component of the Ski complex, have also been linked to syndromic diarrhea/trichohepatoenteric syndrome (SD/THES1) (MIM#222470) (Hartley et al. 2010; Fabre et al. 2011). The human TTC37 (tetratricopeptide repeat domain 37) protein, also known as Thespin (trichohepatoenteric syndrome protein), is the ortholog of the budding yeast scaffolding protein Ski3 and contains 20 predicted TPR (tetratricopeptide repeat) motifs, which typically perform structural roles and mediate protein–protein interactions (Fig. 3C). Based on the crystal structure of the budding yeast Ski complex (Halbach et al. 2013) (PDB# 4BUJ), like Ski3, TTC37 would be predicted to form a scaffold for the Ski2 ortholog, SKIV2L, and the Ski8 ortholog, WDR61 (Fig. 3D).

Exome sequencing of 35 individuals with SD/THES1 from 32 unrelated families identified numerous different mutations in *TTC37* (Table 1; Fig. 3C; Supplemental Table S2; Hartley et al. 2010; Fabre et al. 2011, 2013; Kotecha et al. 2012; Bozzetti et al. 2013; Kammermeier et al. 2014; Chong et al. 2015; Monies et al. 2015; Oz-Levi et al. 2015; Rider et al. 2015; Lee et al. 2016a,b; Kinnear et al. 2017). Like *SKIV2L* mutations, most of the *TTC37* mutations introduce premature termination codons or other mutations predicted to cause loss of TTC37 function (Supplemental Table S2); however, eight missense mutations were identified in 10 affected individuals (Table 1). Four individuals possess homozygous *TTC37* mutations—*TTC37* (L761P, P1270A, or R1503C), three individuals harbor compound heterozygous

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TTC37 mutations—*TTC37* (G673D, L1485R, or L1505S) and *TTC37* (Null allele), and three individuals harbor *TTC37* mutations with only one mutation identified thus far—*TTC37* (A1077D or D1283N) (Table 1; Fig. 3C; Supplemental Table S2). Two individuals with homozygous *TTC37* (R1503C) mutations exhibited the most severe disease (life span ≤5 mo). Based on the yeast Ski complex structure (Halbach et al. 2013), the conserved TTC37-G673, -L761, -A1077, and -P1270 residues, corresponding to Ski3-V811, -V899, -A1155, and -V1422 residues, respectively, could be important for both intramolecular interactions and interactions with Ski8 (Fig. 3D). Notably, the TTC37-P1270/Ski3-V1422 residue is close to a conserved Ski8-binding motif [QRxxΦ(Ski3-1412-1416;TTC37-1260-1264)] (Halbach et al. 2013), suggesting substitution of this residue could alter WDR61/Ski8 binding. The TTC37 residue substitutions, some located in/near TPR motifs, could also impair TTC37 folding/stability. Like SKIV2L variants, no functional studies on TTC37/Ski3 variants linked to SD/THES1 have been performed to date.

Comparisons and potential mechanisms of exosome-linked disease

The greatest surprise about the discovery of mutations in different genes encoding structural subunits of the RNA exosome that cause disease is the fact they induce such varied, tissue-specific phenotypes. Amino acid changes in two similarly located cap subunits of the RNA exosome complex, EXOSC2 and EXOSC3, cause different phenotypes (Figs. 1, 2). *EXOSC2* mutations cause a novel syndrome (retinitis pigmentosa, hearing loss, hypothyroidism, brachydactyly, facial gestalt, premature aging, and mild intellectual disability) with only mild cerebellar atrophy (Di Donato et al. 2016), whereas *EXOSC3* mutations cause pontocerebellar hypoplasia type 1b with severe cerebellar atrophy and spinal motor neuron loss (Wan et al. 2012). Certain amino acids altered in EXOSC2 and EXOSC3 are even found in identical or similar positions in the same domains of these proteins. Compare, for example, EXOSC2-G30 vs. EXOSC3-G31 in the N-terminal domain, as well as EXOSC2-G198 versus EXOSC3-W238 in the KH domain (Fig. 2A,C). In contrast, amino acid changes in the differently located EXOSC3 cap subunit and EXOSC8 ring subunit of the RNA exosome cause similar pontocerebellar hypoplasia (PCH) type 1b and 1c phenotypes, respectively (Figs. 1, 2; Wan et al. 2012; Boczonadi et al. 2014). However, unlike EXOSC3 variants, EXOSC8 variants also cause hypomyelination in addition to PCH (Boczonadi et al. 2014). Notably, like EXOSC2 variants, EXOSC8 variants impair vision and hearing, and some EXOSC3 and EXOSC8 variants confer mitochondrial defects (Boczonadi et al. 2014; Di Donato et al. 2016; Schottmann et al. 2017).

How could amino acid changes in different structural subunits of the RNA exosome lead to such varied, tissue-specific disease? One explanation could be that exosome subunits are expressed and required at different levels in different cell types/tissues and therefore amino acid changes in one exosome subunit could affect one cell type/tissue more than another. However, the human protein atlas shows that EXOSC2, EXOSC3, and EXOSC8 are expressed at medium to high levels in neuronal cells of the cerebral cortex and hippocampus and Purkinje cells of the cerebellum (Uhlen et al. 2015), suggesting that the levels of exosome subunits and the RNA exosome complex are similar in different parts of the brain.

Figure 4 shows three potential molecular mechanisms that could explain how amino acid changes in different structural exosome subunits could alter RNA exosome function to cause tissue-specific disease phenotypes. All these proposed mechanisms would result in impaired RNA processing/degradation by the RNA exosome. In the first mechanism, amino acid changes in exosome subunits could differentially affect the level/stability of the subunit and the assembly/disassembly of the entire RNA exosome complex (Fig. 4A). Tissue-specific phenotypes of the EXOSC2/3/8 variants, such as cerebellar atrophy, might therefore correlate with the level of functional RNA exosome produced. In support of this model, PCH1c-affected individuals with *EXOSC8* mutations not only show reduced levels of EXOSC8 variants but also EXOSC3, suggesting the loss of EXOSC8 leads to a reduction in the amount of other subunits of the RNA exosome complex (Boczonadi et al. 2014). However, thus far, exosome subunit variant levels have only been examined in myoblasts

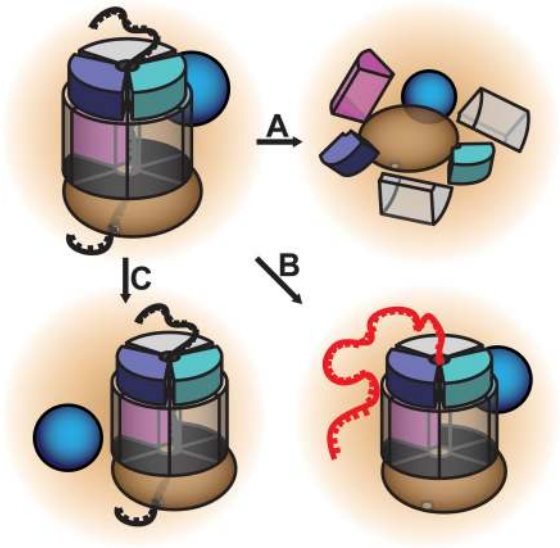

FIGURE 4. Potential mechanisms by which disease-linked amino acid changes in EXOSC2, EXOSC3, and EXOSC8 subunits could impair RNA exosome function and lead to tissue-specific phenotypes and diseases. (*A*) Changes in exosome subunits could disrupt the assembly/disassembly of the RNA exosome complex and impact overall levels of functional complex. (*B*) Changes in exosome subunits could impair interactions or paths for specific RNA targets (red). (*C*) Changes in exosome subunits could impair interactions with exosome cofactors (blue sphere). The EXOSC2 (teal), EXOSC3 (slate blue), and EXOSC8 (magenta) exosome subunits are highlighted.

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and fibroblasts, so further analysis of relevant tissues is required to test this model. As the levels of EXOSC3 variants are also reduced in a neuronal cell line (Fasken et al. 2017), EXOSC3 and EXOSC8 variants could reduce the overall levels of the RNA exosome complex, leading to similar PCH phenotypes. In contrast, EXOSC2 variants might only mildly reduce the overall level of the RNA exosome, causing no PCH phenotype.

In the second mechanism, amino acid changes in exosome subunits could differentially affect the entry paths for and/or interactions with specific RNA substrates of the RNA exosome (Fig. 4B). In the yeast RNA exosome, all three cap subunits (Rrp4, Rrp40, and Csl4) make direct contact with RNA, and the integrity of the S1/KH ring is critical for the path of RNA to the nuclear catalytic subunit, Rrp6 (Makino et al. 2013; Wasmuth et al. 2014). Substitution of conserved RNA-binding residues in the S1 domain of Rrp40 (K107, K108, R110) reduces Rrp6 catalytic activity in the RNA exosome (Wasmuth et al. 2014). In addition, an Rrp43 loop contacts Rrp44/Dis3 and may help to stabilize the direct access or channel-independent path of RNA to Rrp44 (Zinder et al. 2016). Deletion of the Rrp43 loop alters Rrp44 catalytic activity in the RNA exosome (Zinder et al. 2016). The EXOSC2/3/8 variants could therefore differentially alter the paths of RNA to EXOSC10/Rrp6 and DIS3/Rrp44 ribonucleases, if the interactions are conserved.

A good candidate for a specific RNA substrate that could be misprocessed by the RNA exosome containing EXOSC3/8 variants in individuals with pontocerebellar hypoplasia (PCH) type 1b/c is tRNA. In support of this idea, mutations in genes linked to five PCH types (PCH2/4/5/6/10) encode enzymes that process/modify tRNA, including the tRNA splicing endonuclease (TSEN) complex (*TSEN2*; *TSEN34*; *TSEN54*) (Budde et al. 2008), a tRNA synthetase (*RARS2*) (Edvardson et al. 2007), a tRNA synthase (*SEPSECS*) (Agamy et al. 2010), and a TSEN kinase (*CLP1*) (Karaca et al. 2014; Schaffer et al. 2014). In addition, the RNA exosome in budding yeast plays a prominent role in degrading tRNAs (Gudipati et al. 2012; Schneider et al. 2012). The EXOSC3/8 variants could therefore cause PCH1b/c by impairing the degradation of misprocessed tRNAs, leading to the accumulation of misprocessed tRNAs that disrupts translation and neuronal tissue function. The high neuronal demand for mature tRNAs that must be properly localized to synapses for local translation could potentially explain the neuronal-specific effects of EXOSC3/8 variants as well as the other tRNA enzyme variants linked to PCH.

Specific RNA substrate candidates that could be misprocessed by the EXOSC2 variant-containing RNA exosome in individuals possessing the novel syndrome with retinitis pigmentosa are snRNA and pre-mRNA. Notably, mutations in genes encoding splicing factors, such as *PRPF31,* are linked to retinitis pigmentosa (Vithana et al. 2001; Linder et al. 2015) and the yeast RNA exosome processes/degrades snRNAs and pre-mRNA (Allmang et al. 1999a; Bousquet-Antonelli et al. 2000; van Hoof et al. 2000a). The EXOSC2 variants could thus cause a novel syndrome by impairing the processing/degradation of snRNAs and pre-mRNAs, leading to the accumulation of misprocessed snRNA and undegraded pre-mRNA that disrupts splicing and retinal tissue function.

In the third mechanism, amino acid changes in exosome subunits could differentially affect interactions with different exosome cofactors and/or the EXOSC10/Rrp6 ribonuclease subunit itself (Fig. 4C). To date, in elegant structural studies, yeast exosome cofactors have been shown to directly interact with exosome cap subunits, Rrp6, and two ring subunits. In particular, the nuclear Rrp47 cofactor interacts with Rrp6 via intertwined helices that form a composite surface, binding to Mtr4 of the TRAMP complex and other complexes and recruiting Mtr4 to the RNA exosome (Schuch et al. 2014). Furthermore, the nuclear Mpp6 cofactor interacts with the Rrp40 cap subunit and can also recruit Mtr4 to the RNA exosome (Falk et al. 2017; Wasmuth et al. 2017). The cytoplasmic Ski7 cofactor interacts with the Csl4 cap subunit and two ring subunits, Mtr3 and Rrp43 (Kowalinski et al. 2016). Finally, as shown in Figure 1B, the nuclear Rrp6 ribonuclease subunit itself interacts with all three cap subunits, Rrp4, Rrp40, and Csl4, and the same two ring subunits, Mtr3 and Rrp43 (Makino et al. 2013, 2015; Wasmuth et al. 2014). In fact, Ski7 and Rrp6 share a common interaction surface on the yeast RNA exosome (Kowalinski et al. 2016). EXOSC2/3/8 variants could therefore potentially alter interactions with EXOSC10/Rrp6, C1D/Rrp47, hMPP6/Mpp6, or HBS1L3/Ski7 to cause tissue-specific disease, if interactions of the human exosome cofactor orthologs with the human RNA exosome are conserved. As EXOSC10/Rrp6, C1D/Rrp47, and hMPP6/Mpp6 all facilitate recruitment of hMTR4/Mtr4 (Schilders et al. 2007; Lubas et al. 2011; Falk et al. 2017; Wasmuth et al. 2017) and Ski7 interacts with the Ski complex (Araki et al. 2001; Wang et al. 2005; Kowalinski et al. 2016), EXOSC2/3/8 variants could also differentially impair interactions with the NEXT, TRAMP, and Ski complexes to cause disease. Certainly, the EXOSC2/3/8 subunits could also specifically interact with different, as-yet unidentified, tissue-specific exosome cofactors and therefore the EXOSC2/3/8 variants would only affect tissues that harbor a subunit-specific exosome cofactor. Consistent with this model is the recent identification of mutations in RNA exosome cofactor genes. However, additional studies are required to both identify additional exosome cofactors in humans and define the interaction of these cofactors with the RNA exosome.

The three potential molecular mechanisms presented in Figure 4 could all contribute to RNA exosome dysfunction in disease. Certainly, these mechanisms are not mutually exclusive. A major challenge is considering how the requirements for RNA exosome activity could differ across tissue and cell types to manifest as the different disease phenotypes when there are distinct changes within different or even the same RNA exosome subunit.

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Future directions

Major challenges in understanding the function of the RNA exosome still remain. How this complex mediates precise processing of some RNA targets and complete destruction of other RNAs is still poorly understood. Now, with the identification of mutations in the RNA exosome subunit and cofactor genes that cause distinct disease phenotypes, there is a pressing need to understand the function of key conserved amino acid residues within the RNA exosome subunits/cofactors, with the ultimate goal of defining the molecular mechanisms that cause these devastating diseases. Understanding how mutations in the RNA exosome/cofactor genes cause disease requires not only delineating the roles of these subunits/cofactors and specific amino acids within the exosome/cofactor, but also defining the requirements for the RNA exosome and its cofactors in specific cells and tissues. Only when these two key types of information are integrated can the mechanism of disease be defined.

Some approaches that could provide important insights include identifying the RNA exosome cofactors in the specific tissues that are most impacted in disease. In addition, continued structural analysis of the RNA exosome with a focus on the human RNA exosome and its associated cofactors is critical. Efforts will also be required to identify the RNA targets that are most susceptible to the specific disease-causing changes in the RNA exosome/cofactor in the tissues impacted in the disease. These experiments will be challenging as specific regions of the brain, such as the cerebellum, are affected and obtaining the cells/tissue to perform these experiments will not be trivial. Experiments in model organisms will continue to be important to define the functional consequences of the amino acid changes in RNA exosome subunits/cofactors that have been linked to disease.

The identification of disease-causing mutations in RNA exosome subunit genes was initially surprising, with the first such mutation in *EXOSC3* reported in 2012 (Wan et al. 2012). However, mutations in additional exosome genes, *EXOSC2* and *EXOSC8*, as well as exosome cofactor genes, *RBM7*, *SKIV2L*, and *TTC37*, have been identified in less than five years since the original report (Hartley et al. 2010; Fabre et al. 2012; Boczonadi et al. 2014; Di Donato et al. 2016; Giunta et al. 2016). Such rapid discoveries suggest it is highly likely that other RNA exosome subunit/cofactor genes will be linked to disease in the near future. On this note, in a very recent report, a homozygous mutation in *EXOSC9* (yeast *RRP45*) (Burns et al. 2017), encoding another exosome ring subunit, has been linked to a novel form of cerebellar hypoplasia/atrophy. Thus, there is much still to be learned about the multifaceted functions of the RNA exosome and its cofactors and this knowledge should provide new insights into the mechanisms of RNA exosome-linked disease.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article.

ACKNOWLEDGMENTS

We thank our colleagues Elena Conti, Christopher D. Lima, and Ambro van Hoof for sharing their expertise in analysis of the RNA exosome as well as members of the Corbett laboratory for helpful discussions and comments. This work was supported by both a National Institutes of Health R01 grant (GM058728) and National Institutes of Health R21 grant (AG054206) to A.H.C., and both a National Institutes of Health F32 grant (GM125350) and a Postdoctoral Enrichment Award from the Burroughs Wellcome Fund to D.J.M. D.J.M. was also supported by Emory University, Institutional Research and Academic Career Development Award (IRACDA), Fellowships in Research and Science Teaching (FIRST) Postdoctoral Fellowship.

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RNA 2018 24: 127-142 originally published online November 1, 2017
Access the most recent version at doi:10.1261/rna.064626.117

Supplemental Material http://rnajournal.cshlp.org/content/suppl/2017/11/01/rna.064626.117.DC1

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