# RNAs of the human chromsome 15q11-q13 imprinted region

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## Abstract

The human chromosome 15q11-q13 region hosts a wide variety of coding and non-coding RNAs, and is also the site of nearly every imaginable type of RNA processing. To deepen the intrigue, the transcripts in the human chromosome 15q11-q13 region are subject to regulation by genomic imprinting, and some of these transcripts are imprinted in a tissue-specific manner. Since the region is critically important for three human neurogenetic disorders, Angelman syndrome, Prader-Willi syndrome, and 15q duplication syndrome, there is intense interest in understanding the types of RNA and RNA processing that occurs among the imprinted genes. This review summarizes what is known about the various RNAs within the imprinted domain, including a novel type of RNA that was only very recently identified.

## THE CHROMOSOME 15Q11-Q13 REGION AND ASSOCIATED HUMAN DISORDERS

The human chromosome 15q11-q13 region is a 6 Mb segment of the genome that is centrally involved in three human neurogenetic disorders: Prader-Willi syndrome (PWS), Angelman syndrome (AS) and 15q duplication syndrome (reviewed in[1]). In addition to its relevance for human disease, this region hosts a variety of unique gene regulation paradigms, the most notable of which is genomic imprinting, an epigenetic phenomenon by which genes are expressed preferentially from only one parental allele The genomic organization and regulation of imprinted expression is conserved on the syntenic region of mouse chromosome 7C[2,3]. Through a variety of studies in both mouse and human systems, much has been learned about this region.

Imprinted genes are usually clustered and utilize a variety of mechanisms to establish and maintain their imprinted status, including differential DNA methylation, differential histone modification, and antisense transcription. Within the 15q11-q13 region there are at least 14 imprinted transcripts: *MKRN3, MAGEL2, NDN, PWRN1, C15ORF2/NPAP1, SNURF-SNRPN, SNORD107/HBII-436, SNORD64/HBII-13, SNORD108/HBII437, SNORD109A/HBII438A, SNORD116/HBII-85, IPW, SNORD115/HBII-52, SNORD109B/HBII-438B, UBE3A*, and *ATP10A*. Most of these genes are expressed exclusively from the paternally inherited allele in somatic tissues. *UBE3A* and *ATP10A* show brain-specific imprinted expression and are the only imprinted genes in the region that are expressed from the maternally inherited allele. Moreover, *ATP10A* does not show imprinted expression in all individuals[4].

The imprinted domain is flanked by non-imprinted genes: *TUBCGP5, CYFIP1, NIPA2,* and *NIPA1* that are proximal to the imprinted domain[5] and *GABRB3, GABRA5, GABRG3, OCA2,* and *HERC2* that are distal to the imprinted domain[6]. Most individuals with PWS and AS have a large deletion of the 15q11-q13 region[7]. Depending on their specific deletion

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breakpoints, individuals with PWS or AS also may be lacking one copy of some or all of the non-imprinted genes in the region[8–10]. In this review, we focus only on the imprinted domain of the chromosome 15q11-q13 region.

## Genomic imprinting at chromosome 15q11-q13

Genomic imprinting in the chromosome 15q11-q13 region is controlled by a bipartite imprinting center (IC)[11,12]. One element in this imprinting center, termed the Prader-Willi syndrome imprinting center, or PWS-IC, includes the major promoter and exon 1 of the *SNURF-SNRPN* gene. Within the PWS-IC lies a differentially-methylated CpG island that is methylated on the maternally-inherited allele and unmethylated on the paternally-inherited allele. PWS individuals with small deletions that include the PWS-IC and mouse models have functionally defined the PWS-IC and determined it to lie within an approximately 5 kb region (4.3 kb in humans and 6 kb in mouse)[12,13]. In addition to the *SNURF-SNRPN* major promoter and exon 1, this region is thought to include an additional element that is necessary for full PWS-IC function[14].

The second element in the bipartite imprinting center is the Angelman syndrome imprinting center, or the AS-IC. While the mechanism by which this element functions is not known, the AS-IC is thought to repress the activity of the PWS-IC in the maternal germline, thereby facilitating the methylation of the maternal allele of the PWS-IC in this lineage and during subsequent development. Recent data using the mouse model system postulates that the AS-IC establishes the maternal imprint by driving expression from the upstream exons of *SNURF-SNRPN* in the maternal germline[15].

The bipartite imprinting center executes its function amidst several allele-specific covalent histone modifications and other chromatin features. The maternally inherited PWS-IC is marked with tri-methylated histone H3, lysine 9 (H3K9me3), while the paternally inherited PWS-IC is marked with di- and tri-methylated histone H3 lysine 4(H3K4me2 and me3) as well as acetylated histones H3 and H4[16,17]. Mouse studies have determined that H3K36me3 unexpectedly marks the repressed maternal allele, along with the expected repressive histone modifications, H4K20me3, H3K9me3, and H3K79me3[18].

## Human-Mouse shared synteny

A region on mouse chromosome 7C is orthologous to the human chromosome 15q11-q13 region[3] (Figure 1). The gene structure and regulation of genomic imprinting is exquisitely maintained between human and mouse, with a few exceptions. One protein-coding gene, *Frat3*, is imprinted in mouse, but not present in human[19]. Conversely, *C15ORF2/NPAP1* is imprinted in humans, but is not present in mouse[20]. Another gene *ATP10A*, is imprinted in some human individuals, but not imprinted in mouse[4,21]. There are several annotated non-coding RNAs, however, that are not conserved between the two species. Whether these RNAs exist in both species, but are poorly annotated or are structurally different and therefore not recognized as being the same ncRNA is unclear. These ncRNAs will be further discussed below.

The expression pattern of the genes also differs between mouse and human (compare Figure 1A and B). In mouse, only the protein-coding portion of *Snurf-Snrpn* is expressed in multiple tissues; all other known paternally expressed genes in the region, are expressed exclusively in the brain. Therefore, most of the murine genes in the mouse 7C imprinted region exhibit brain-specific expression (Figure 1A). In human, the protein coding *SNURF-SNRPN* transcript, as well as the ncRNAs between the end of the protein coding gene and *IPW* are expressed in a variety of cell types. Furthermore, the proximal genes, *NDN* and *MKRN3* are also expressed in a variety of cell types. Only the portion of the *SNURF-*

*SNRPN* transcript distal to *IPW*, some upstream exons of *SNURF-SNRPN*, and *MAGEL2* are brain-specific (Figure 1B).

## GENES AND GENE EXPRESSION

Nearly every type of RNA and/or gene can be found in the chromosome 15q11-q13 imprinted region. These RNAs employ a variety of processing mechanisms, including alternative splicing, alternative polyadenylation, and exonucleolytic processing from introns, as well as undetermined mechanisms involving antisense transcription and resulting gene silencing. The details of the RNAs and what is known about their processing is described below and summarized in Tables 1–3.

### Protein coding transcripts

**Intronless genes located in proximal 15q11-q13—***MKRN3, MAGEL2, NDN*, and *C15ORF2/NPAP1* are located in a cluster at the proximal end of human chromosome 15q11-q13 and at the distal end of the syntenic region on mouse chromosome 7C. *MKRN3* and *NDN* each have differentially methylated CpG islands at their respective promoters that are methylated on the maternally inherited allele and unmethylated on the paternally inherited allele[22,23]. Data from individuals with atypical deletions or translocations suggest that these three genes are not responsible for the major features associated with PWS[24]. One PWS individual was reported to have a deletion that does not include the *MKRN3, MAGEL2*, or *NDN* genes, and showed *NDN* expression in a patient-derived lymphoblastoid cell line. DNA methylation at the *NDN* promoter was also consistent with expression from the paternally inherited allele. Another individual was reported with a translocation that resulted in the deletion of the paternal copies of *MKRN3, MAGEL2*, and *NDN*, however, this individual did not have PWS[24].

*MKRN3* (makorin ring finger protein 3) encodes a probable ubiquitin ligase and is one of four members of the makorin family of zinc finger proteins[25]. *MKRN3* has a typical C3HC4 zinc finger, which comprises the RING domain and confers ubiquitin ligase activity. Notably, *MKRN3* is specific to therian mammals, where it is imprinted[22,25]. There is also a ncRNA that is antisense to *MKRN3*.

*MAGEL2* encodes a melanoma antigen gene-encoding (MAGE)-like protein that is also known as Necdin-like *1* (*NDNL1*) due to its similarity to *NDN*[26]. *Magel2* has been disrupted by targeted mutation in mouse[27]. Mice deficient for *Magel2* exhibit neonatal growth retardation, excessive weight gain, increased adiposity, hypophagia, altered metabolism, disrupted circadian rhythms, and impaired reproductive function[27–29].

*NDN* (Necdin) encodes another MAGE-like protein that is thought to function as a growth suppressor in neuronal and non-neuronal cells[30]. *Ndn* binds to the transactivation domain of E2F1 and is thought to facilitate exit of the cell from the cell cycle through this mechanism[31]. However, NDN also interacts with SIRT1 and mediates the deacetylation of p53, which may also mechanistically explain the regulation of the cell cycle[32]. Disruption of the murine *Ndn* gene has led to conflicting results. One group reported that *Ndn*-deficient mice exhibited postnatal lethality, skin scraping, and increased spatial learning[33]. Another group reported postnatal lethality due to respiratory defects[34]. A third group reported no obvious phenotype associated with targeted mutation of *Ndn*[35]. Using these mouse models, roles for N*dn* in myoblast differentiation, axonal outgrowth and migration, adipogenesis, tumor suppression, and modulation of the thyroid axis have all been reported[36–41].

*C15ORF2/NPAP1* is a protein-coding gene that is primate-specific and has undergone positive selection during evolution[42]. *C15ORF2/NPAP1* consists of a single exon of 8 kb

that is predicted to encode a 1156 amino acid protein. The presence of a long terminal repeat sequence in the 3' end of the gene suggests that it may have arisen in the primate lineage due to retroviral integration[43]. The mRNA is expressed in brain and testes[20]. Preliminary work using an antibody raised against C15ORF2/NPAP1 suggests that it is expressed in various regions of the brain, including the hypothalamus, and is slightly larger than 130 kDa[42]. The function of the protein is not known, although it was recently shown to be associated with the nuclear pore complex[44].

While *MKRN3, MAGEL2,* and *NDN* are conserved between human and mouse, *Frat3* is not. *Frat3* arrived in the imprinted domain on mouse chromosome 7C by a recent retrotransposition event and is most likely imprinted due to its fortuitous location in an imprinted region[19]. Very little is known about *Frat3*, however it is most similar to *Frat1* and *Frat2*, GSK3-binding protein family members that are known to positively regulate Wnt signaling[45]. *Frat3* does not exist in the human genome[19].

**SNURF-SNRPN**—The *SNURF-SNRPN* gene encodes a bicistronic transcript that produces two proteins: SNURF and SNRPN[46]. SNRPN is a small nuclear ribonucleoprotein that functions in pre-mRNA processing, and perhaps alternative splicing[47]. SNURF is a nuclear localized protein of unknown function that is produced from the first three exons of the *SNURF-SNRPN* transcript[46]. The major promoter and first exon of *SNURF-SNRPN* comprise the PWS-IC and is necessary for the expression of all of the paternally expressed genes in the 15q11-q13 imprinted region[13]. Targeted mutations of the *Snurf* and *Snrpn* genes have no obvious phenotype, as long as they do not disrupt the imprinting center[48,49]. However, a 6 kb deletion that includes the promoter and first exon of the *Snurf-Snrpn* transcript is sufficient to lead to an imprinting defect in mice and loss of expression from all paternally expressed genes in the region[13]. The *SNURF-SNRPN* gene also produces a long, ncRNA and is subject to extensive alternative splicing at the 5' and 3' ends[50]. The *SNURF-SNRPN* transcript will be further discussed below.

**UBE3A**—The *UBE3A* gene encodes an E3 ubiquitin ligase, known as E6-associated protein (E6AP)[51]. The *UBE3A* mRNA has at least 7 reported isoforms that arise from alternative splicing[52]. Most of the transcript variation resides in the 5' end of the transcript. There is an antisense transcript to *UBE3A* (*UBE3A-ATS*, discussed further below) that most likely regulates its imprinted expression by leading to repression of paternal *UBE3A*[53–55]. The loss function from the maternal allele of *UBE3A* causes Angelman syndrome[56].

The E6AP protein is the prototypical HECT (homologous to E6AP carboxyl terminus) domain ubiquitin ligase. It functions to recognize target substrates and transfer ubiquitin moieties from the E2 ubiquitin-conjugating enzymes to them. E6AP has been found in the cytoplasm and nucleus and is expressed in a broad range of tissues. Three different protein isoforms, differing in the extreme N-termini have been reported and are hypothesized to mediate different target substrate specificities, although this has not been demonstrated[57]. Mice deficient for *Ube3a* have seizures (strain dependent), deficits in LTP and LTD, poor performance on the rotarod, and loss of plasticity in the visual cortex[58–61].

## Non-coding RNAs

The most intriguing aspect of the chromosome 15q11-q13 region is the variety of non-coding RNAs (ncRNAs) that can be found. Long non-coding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs), small nucleolar long non-coding RNAs (snolncRNAs), microRNAs (miRNAs), and PIWI-interacting RNAs (piRNAs) have all been identified in the imprinted domain. There are also at least two known cases of antisense transcription, and

function has been ascribed to one of them. Furthermore, both alternative splicing and alternative promoter usage appear to play roles in regulation of expression within the region.

**lncRNAs—**The annotated human lncRNAs include *PWRN2, PWRN1, PAR-SN, PAR5, HBT8, IPW, PAR1*, and *PAR4*. Additionally, three other lncRNAs, *MKRN3AS, PWCR1*, and *UBE3A-ATS*, have been reported in the literature, but are currently not annotated in RefSeq or the UCSC Genome Browser. All but two of these lncRNAs (*MKRN3AS* and *PWRN2*) are part of the non-coding portion of the *SNURF-SNRPN* transcript. *PWRN1, PAR-SN, PAR5, HBT8, IPW, PAR4*, and *UBE3A-ATS* have all been reported to be part of the *SNURF-SNRPN* transcript, and thus may be nothing more than spliced or unspliced variants of that transcript[20,62,63]. However, since the processing of the *SNURF-SNRPN* transcript is not fully understood, it is not clear whether any of these transcripts have independent functions. The lncRNAs are not as conserved in mouse: only four of the human lncRNAs *MKRN3AS, PWCR1, IPW*, and *UBE3A-ATS* are present in the mouse chromosome 7C region, and they have very little sequence conservation. Conversely, putative murine lncRNAs include twelve annotated, but un-named transcripts in addition to the aforementioned transcripts. Seven of 16 murine lncRNAs appear to be derived from the *Snurf-Snrpn* transcript.

*MKRN3AS* is the most proximal lncRNA and its function is unknown. The mRNA for *MKRN3AS* has been reported to be approximately 7.1 kb, containing two exons[22]. *MKRN3* and *MKRN3AS* overlap completely, with 1 kb of the 3' end of *MKRN3* extending into the intron of *MKRN3AS*. Murine *Mkrn3as* has also been identified. The splice acceptor site is conserved between mouse and human, but a full-length transcript has not been identified[64].

*PWRN2* and *PWRN1* are proximal to the PWS-IC in humans, but do not exist in mice. *PWRN2* and *PWRN1* are alternatively spliced and polyadenylated non-coding RNAs that lie between *C15ORF2* and *NDN*[20]. *PWRN2* and *PWRN1* were originally identified using in silico searches of two databases. *PWRN2* spans 7.2 kb of genomic DNA consisting of three exons. *PWRN1* spans 160 kb of genomic DNA and 26 exons. Both genes have been partially duplicated: *PWRN1* and *PWRN2* each have 5 partially duplicated copies. The *PWRN1* copies lie proximal to the *PWRN1* gene, and the *PWRN2* copies lie both proximal and distal to *PWRN2*. Both genes are most highly expressed in testes, but *PWRN1* can also be detected at low levels in prostate, heart, liver, lung, trachea, spinal cord, and fetal brain[20]. The 3' exons of *PWRN1* have also been identified as part of the *SNURF-SNRPN* transcript in brain, and thus *PWRN1* may represent more upstream exons of this very long transcript[42]. *PWRN2* is expressed from both parental alleles in testes, and therefore does not seem to be imprinted. However, this tissue has undergone resetting of the imprint, so it is not known whether *PWRN2* bears the epigenetic marks of imprinted genes or whether it is imprinted in other tissues that have not been analyzed to date[20].

The *SNURF-SNRPN* transcript is complicated and unique. It not only produces a bicistronic message that encodes the SNURF and SNRPN proteins (discussed above)[46], but it also comprises many other lncRNAs. Altogether, the human *SNURF-SNRPN* transcript spans approximately 600 kb of genomic DNA and has in excess of 148 exons[50]. *SNURF-SNRPN* undergoes extensive alternative splicing, the extent of which is not fully understood.

At the 5' end, alternative upstream exons or alternative promoters are preferentially used in brain and perhaps germ cells[15,65–68]. As many as 9 upstream exons have been identified that span approximately 150kb of genomic distance upstream of *SNURF-SNRPN* exon 1[67]. These upstream exons are similar to one another and also harbor CpG islands, two of which show the same methylation pattern as the PWS-IC (maternally methylated and paternally unmethylated), while the third shows the opposite pattern of methylation, being maternally

unmethylated and paternally methylated[67]. One putative function of these upstream exons may be to regulate expression of the *SNURF-SNRPN* non-coding RNAs[50,68]. Interestingly, one of the alternative upstream exons is included within the smallest region of deletion overlap for AS imprinting center mutations, and may play a role in the function of the AS-IC[67]. A recent publication suggests that the AS-IC may function by promoting transcription from the upstream alternative exons in the female germline[15].

How the *SNRPN* transcript extends distally of the polyadenylation site(s) at the 3' end of the coding portion of the gene is not known. Transcription through the polyadenylation site(s) of *SNRPN* occurs in most tissues in humans, but does not occur in mouse, except for in brain. In most human tissues, the non-coding RNAs downstream of *SNRPN*, but ending with *IPW* are expressed[50,69–71]. While it is known that much of this non-coding transcript serves as a host for snoRNAs[70] and a newly identified class of RNAs termed snolncRNAs(further discussed below), there are also transcripts of unknown function, including *PAR-SN, PAR5*, and *HBT8*. These RNAs are annotated to be approximately 1.7, 3.4, and 4.1 kb in size, respectively, although by northern blot, a *PAR5* probe recognizes an approximately 12kb band in skeletal muscle and a diffuse smear in brain[62], and a *PAR-SN* probe recognizes a 3kb band in brain, heart, and skeletal muscle[63]. *HBT8* was identified as an mRNA that encodes a short peptide expressed in brain, however the protein-coding potential of this transcript has not been verified. While these transcripts do seem to be part of distinct non-coding RNAs, it is also possible that they are simply non-functional exons within the *SNURF-SNRPN* non-coding transcript.

*IPW* is a non-coding transcript that is present in both mouse and human. The non-coding *SNURF-SNRPN* transcript is terminated at or upstream of *IPW* in most human cell types. In brain only, the transcript extends distal to *IPW*[50,69–71]. The *IPW* RNA itself is spliced and consists of three exons in humans and six exons in mouse[69,72]. The human IPW gene produces two transcripts of 2.4 kb and 1.3 kb in most tissues. In brain, however, only the 2.4 kb band is detectable[69]. Analogous RNAs in mouse have not been identified—by northern blot, murine Ipw seems to exist as a high-molecular weight smear. *IPW* is poorly conserved in mammals, except for an approximately 2 kb portion, which shows considerable conservation[72]. The function of *IPW* is also not known. It may only be an exon within the *SNURF-SNRPN* transcript[50].

The 3' end of the *SNURF-SNRPN* non-coding transcript, distal to *IPW*, is only expressed in brain. While this portion of the transcript largely serves as a host transcript for the *SNORD115/HBII-52* snoRNAs[70] (further discussed below), other non-coding RNAs are generated from this transcript, including *PAR1, PAR4*, and *UBE3A-ATS*. *PAR1* and *PAR4* are intronless non-coding RNAs of unknown function that are annotated to be 2.4 kb and 342 bp, respectively. Northern blot analysis using a probe for *PAR1* detects a high molecular weight smear in brain only[62], and therefore may simply be one exon in the brain-specific portion of the *SNURF-SNRPN* non-coding transcript, although it does not seem to be part of any known splice forms in the region. *PAR4* is located in the midst of the *SNORD115/HBII-52* cluster and in fact contains *SNORD115-23*. Portions of *PAR4* are repeated throughout much of the *SNORD115/HBII-52* cluster, suggesting that *PAR4*, too, may be little more than one exon within this transcript.

The generation of *UBE3A-ATS* may be the evolutionary purpose for the brain-specific portion of the *SNURF-SNRPN* transcript. *UBE3A-ATS* refers to the part of the *SNURF-SNRPN* transcript that overlaps the *UBE3A* gene. *UBE3A-ATS* was first observed as an unspliced portion of the *UBE3A* transcript that was reduced in PWS brain, but strongly present in AS brain[53]. Subsequently, murine *Ube3a-ats* was found to be controlled by the PWS-IC, and mice with a paternal deletion of PWS-IC showed reactivation of paternal

*Ube3a* in the brain[54]. These data suggest that expression of the *UBE3A-ATS* leads to the repression of paternal *UBE3A* in the brain. A recent paper by Meng et al. confirmed this finding by showing that termination of murine *Ube3a-ats* results in reactivation of paternal *Ube3a*[55]. This paper also characterized the murine transcript. They reported that *Ube3a-ats* is a non-polyadenylated RNA polymerase II transcript with a relatively short half-life. This and other reports showed that *Ube3a-ats* is transcribed across the entire *Ube3a* gene, even overlapping the promoter[55,65,73]. There are several mechanism by which *UBE3A-ATS* could repress paternal *UBE3A*, including the following possibilities: 1.) *UBE3A-ATS* RNA could recruit repressive histone modifications to the paternal *UBE3A* promoter (or other regulatory element), 2.) the *UBE3A-ATS* transcript could establish a repressive three-dimensional chromatin structure across the paternal allele, or 3.) the act of transcription through the paternal *UBE3A* locus in an antisense direction could cause transcriptional interference. These possibilities are not necessarily mutually exclusive and are an intense area of investigation.

**snoRNAs**—One major function of the *SNURF-SNRPN* non-coding transcript is to generate 72 C/D box small nucleolar RNAs (snoRNAs)[50,70]. These snoRNAs are processed from the introns of the host transcript and are conserved between mouse and human. The snoRNAs fall into 6 groups: *SNORD107/HBII-436, SNORD64/HBII-13, SNORD108/ HBII-437, SNORD109/HBII-438* (2 members), *SNORD116/HBII-85* (29 members), and *SNORD115/HBII-52* (48 members). SnoRNAs feature a C box denoted by the sequence UGAUGA and a D box denoted by the sequence CUGA, and often they contain C' and D' boxes, which are replicas of the C and D boxes, respectively. Immediately adjacent to the D and D' boxes lie antisense boxes. SnoRNAs typically add 2'-O-methyl groups or pseudouridine to ribosomal RNAs and/or spliceosomal RNAs in a sequence-specific manner that is encoded by the sequence of the antisense box. The antisense boxes for the snoRNAs within the human chromosome 15q imprinted region and syntenic mouse region on chromosome 7C are not obviously complimentary to ribosomal RNAs or to spliceosomal RNAS, and thus they have been deemed orphan snoRNAs. Instead, it has been suggested that they may modify mRNAs[70].

Little is known about most of the snoRNAs in this region. The most highly studied snoRNA, *SNORD115/HBII-52*, has an antisense box that is identical among all 48 members of the cluster[70]. Furthermore, this antisense box sequence is also completely conserved in the mouse. The reason for the extensive conservation may be that this snoRNA has been shown to bind and alter post-transcriptional modification of the RNA encoding the serotonin receptor, *HTR2C*[70,74]. It has been proposed that *SNORD115/HBII-52* may work by preventing ADAR2-mediated RNA editing at specific sites in the *HTR2C* RNA[75]. However, it is not clear whether *SNORD115/HBII-52* is performing this function in humans[76].

It has also been proposed that the chromosome 15q11-q13 snoRNAs may be further processed into sno-derived RNAs, or sdRNAs[77]. These sdRNAs show complementarity to sequences near splice junctions, and thus have been hypothesized to influence alternative splicing of specific genes outside of the chromosome 15 region. Recently, it was shown that in addition to the non-canonical snoRNAs that likely modify mRNAs *in trans*, that the chromosome15q snoRNAs also make canonical snoRNAs that modify ribosomal RNAs[78].

**Sno-lncRNAs**—A novel form of small RNA, termed sno-lncRNA (small nucleolar long non-coding RNA), has been very recently discovered in the human chromosome 15q11-q13 region[79]. Sno-lncRNAs are non-coding RNAs that are flanked by snoRNAs. These unique RNAs form where two snoRNAs lie within a single intron. SnoRNAs are processed from introns by exonucleolytic cleavage that is limited by the snoRNPs (small nucleolar ribonucleoproteins) that are recruited to and assembled onto the snoRNA. Sno-lncRNAs are

processed from introns similarly, however, the intervening sequence between the two snoRNAs is also protected from exonucleolytic cleavage. The result is a highly stable, non-coding RNA of variable length that has snoRNA sequences and bound snoRNP proteins at either end. The function of these sno-lncRNAs is unknown, however, the sno-lncRNAS in the chromosome 15 region appear to bind the RNA binding protein, RBFOX2, and may influence alternative splicing by titrating the available levels of this known alternative splice factor[79].

**miRNAs and piRNAs—**There is one known miRNA[80] and a cluster of 17 piRNAs located[81] within the chromosome 15q11-q13 imprinted region in humans. The human miRNA, *miR4508* lies proximal to *MKRN3* and may be transcribed as part of the *MKRN3AS* transcript. This miRNA is not conserved in mouse, however. The human piRNA cluster is located within the *C15ORF2/NPAP1* gene. Three piRNAs in this cluster match the long terminal repeat sequence in the 3' end of the gene, suggesting that *C15ORF2/NPAP1* may be recognized as an invasive gene, and may be silenced by RNA mediated mechanisms[43]. In mouse, a cluster of 10 miRNAs reside in approximately 400 kilobases of genomic sequence between *Ndn* and *Snurf-Snrpn*[82]. The expression patterns and functions of these miRNAs are not known.

## CONCLUSIONS

The imprinted region of chromosome 15q11-q13 harbors a wide variety of RNAs from canonical protein-coding transcripts to novel non-coding RNAs of unknown function. The *SNURF-SNRPN* gene alone accounts for a bi-cistronic transcript, an antisense transcript, lncRNAs of unknown function, snoRNAs, and a novel RNA species called sno-lncRNAs, and is important for three human neurogenetic disorders, Prader-Willi syndrome, Angelman syndrome, and 15q duplication associated autism. How the processing of these multitude RNAs are involved in the human disorders is still not fully known. Studies comparing the neuronal versus non-neuronal RNAs across the region in both human and mouse will undoubtedly shed some light on this complex and interesting genetic region.

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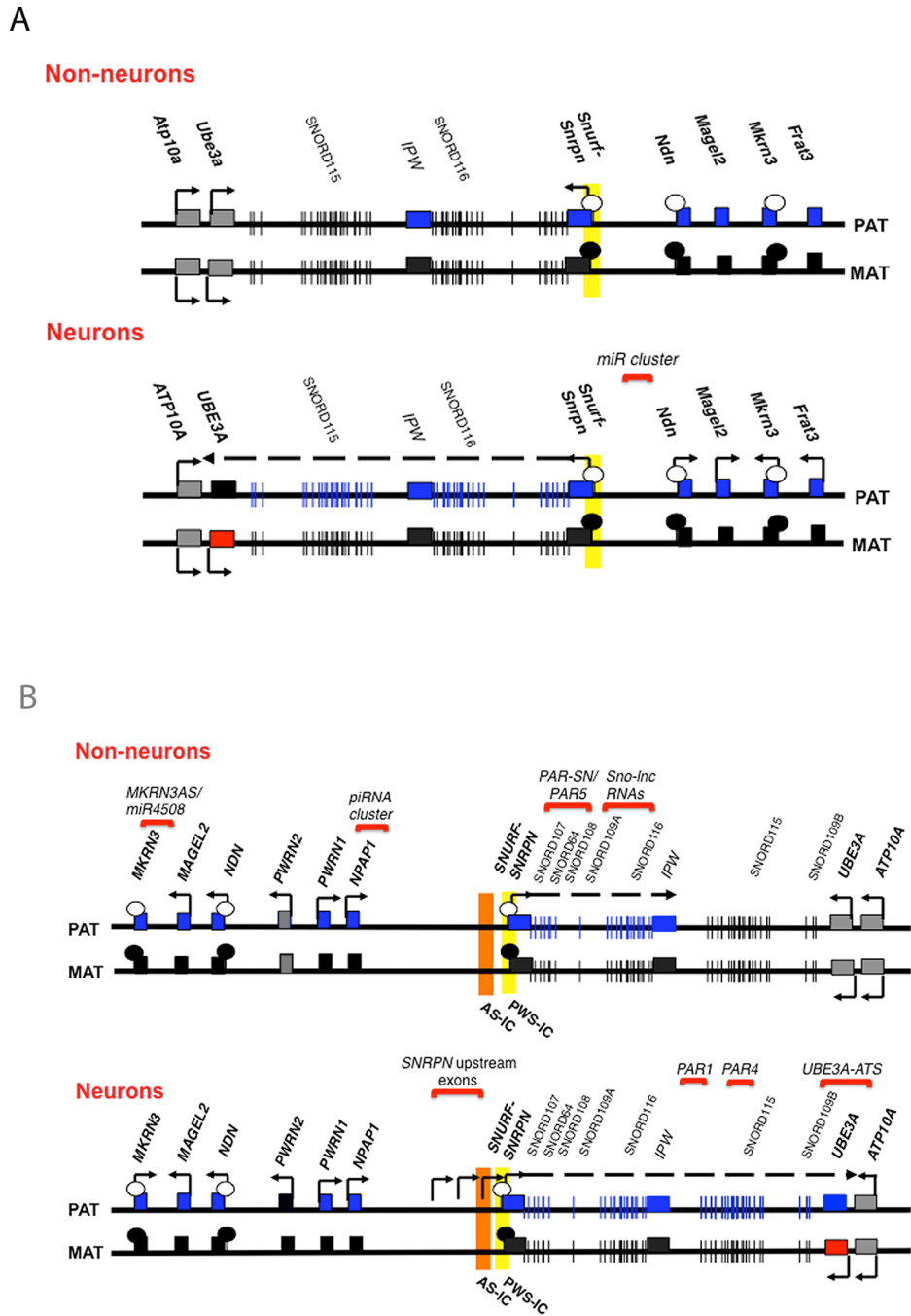
**Figure 1. Maps of the human chromosome 15q11-q13 region and the mouse syntenic region on chromosome 7C**

A.) Map of the mouse chromosome 7C region indicating gene expression patterns in non-neurons (top) and neurons (bottom). B.) Map of the human chromosome 15q11-q13 imprinted region indicating gene expression patterns in non-neurons (top) and neurons (bottom). Blue rectangles represent imprinted transcripts that are paternally expressed, red rectangles represent imprinted transcripts that are maternally expressed, black rectangles represent the repressed alleles of imprinted genes, and grey rectangles represent transcripts that are not imprinted. Maps are not to scale and not intended to be all-inclusive.

**Table 1**

### Protein-coding genes

| Gene name | Position | Function | Ref. |
|---|---|---|---|
| *Peg12/Frat3* | Mm. chr7:69,606,757-69,609,396 | GSK3-binding protein family members | 19 |
| *MKRN3* | Hs. chr15:23,810,454-23,813,166<br>Mm. chr7:69,562,479-69,565,025 | Makorin-ring protein, probable ubiquitin ligase | 21,24 |
| *MAGEL2* | Hs. chr15:23,888,696-23,892,993<br>Mm. chr7:69,521,865-69,526,526 | Melanoma antigen gene-encoding (MAGE)-like protein | 25–28 |
| *NDN* | Hs. chr15:23,930,554-23,932,450<br>Mm. chr7:69,493,163-69,494,813 | May suppress growth in post-mitotic neurons | 29–40 |
| *NPAP1/C15ORF2* | Hs. chr15:24,920,541-24,928,593 | Nuclear pore-associated protein | 41–44 |
| *SNURF* | Hs. chr15:25,200,070-25,213,976<br>Mm. chr7:67,140,305-67,150,042 | Function unknown | 46 |
| *SNRPN** | Hs. chr15:25,200,070-25,223,729<br>Mm. chr7:67,127,388-67,150,042 | Member of the small nuclear ribonucleoprotein complex | 46,47 |
| *UBE3A* | Hs. chr15:25,582,396-25,684,175<br>Mm. chr7:66,484,120-66,562,097 | Ubiquitin E3 ligase | 51–61 |
| *ATP10A* | Hs. chr15:25,923,860-26,108,349<br>Mm. chr7:65,913,572-66,084,796 | phospholipid-transporting ATPase | 4,20 |

**Table 2**

**Large non-coding RNAs**

*SNURF-SNRPN, IPW*, and *UBE3A-ATS* sizes are approximate.

| Gene name | Position | Size | Ref. |
|---|---|---|---|
| *MKRN3-AS* | Hs. unknown<br>Mm. unknown | Unknown<br>Unknown | 21,62 |
| *PWRN2* | Hs. chr15:24,409,926-24,415,053 | 5,128 bp | 43 |
| *PWRN1* | Hs. chr15:24,803,304-24,832,926 | 29,623 bp | 43 |
| *SNURF-SNRPN* | Hs. chr15:25,068,063-25,687,473<br>Mm.chr7:66,484,149-67,293,246 | ~616,500 bp<br>~809,000 bp | 15, 46–50, 63–66 |
| *PAR-SN*[**] | Hs. chr15:25,227,141-25,228,937 | 1,797 bp | 69 |
| *PAR5*[**] | Hs. chr15:25,230,007-25,233,379 | 3,373 bp | 68 |
| *HBT8*[**] | Hs. chr15:25,277,534-25,281,635 | 4,102 bp | http://genome.ucsc.edu |
| *IPW*[**] | Hs. chr15:25,361,711-25,367,655<br>Mm. chr7:66,875,161-66,937,474 | 5945 bp<br>62,314 bp | 70–71 |
| *PAR1*[**] | Hs. chr15:25,380,789-25,383,200 | 2,412 bp | 68 |
| *PAR4*[**] | Hs. chr15:25,456,839-25,457,180 | 342 bp | 68 |
| *UBE3A-ATS*[**] | Hs. chr15:25,582,436-25,684,806<br>Mm. chr7:66,484,028-66,562,559 | ~102,500 bp<br>~78,500 bp | 53–55<br>63,72 |

[**] denotes lncRNAs that are part of the *SNURF-SNRPN* transcriptional unit, therefore, the size of the *SNURF-SNRPN* RNA includes the lncRNAs marked with two asterisks.

<div align="center">

**Table 3**

**Small non-coding RNAs**

</div>

Sno-lnc RNAs range in size from 1,178 nucleotides to 2,859 nucleotides, and are therefore not technically small non-coding RNAs, however, due to their relationship to snoRNAs, they are included in this table.

| Gene name | Position | copies | Ref. |
|---|---|---|---|
| *snoRNAs* | | | 50,67, 73–75 |
| *SNORD107/HBII-436* | Hs. chr15:25,227,141-25,227,215 | 1 | |
| *SNORD64/HBII-13* | chr15:25,230,247-25,230,313 | 1 | |
| *SNORD108/HBII-437* | chr15:25,232,072-25,232,140 | 1 | |
| *SNORD109A/HBII-438A* | chr15:25,287,121-25,287,187 | 1 | |
| *SNORD116/HBII-85** | chr15:25,296,701-25,352,633 | 29 | |
| *SNORD115/HBII-52** | chr15:25,417,020-25,516,600 | 48 | |
| *SNORD109B/HBII-438B* | chr15:25,523,490-25,523,556 | 1 | |
| *sno-lncRNAs* | | | 78 |
| *SNOLNCRNA1* | Hs. chr15:25,310,172-25,313,029 | 1 | |
| *SNOLNCRNA2* | chr15:25,324,204-25,325,380 | 1 | |
| *SNOLNCRNA3* | chr15:25,330,531-25,331,761 | 1 | |
| *SNOLNCRNA4* | chr15:25,332,808-25,334,043 | 1 | |
| *SNOLNCRNA5* | chr15:25,344,645-25,346,822 | 1 | |
| *miRNAs* | | | 79,81 |
| *miR4508* | Hs. chr15:23,807,209-23,807,278 | 1 | |
| *miR344* | Mm. chr7:68,830,112-69,194,754 | 10 | |
| *piRNAs* | Hs. chr15:24,920,541-24,928,593 | 17 | 42,80 |