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Bidirectional transcription from human *LRRTM2*/*CTNNA1* and *LRRTM1*/*CTNNA2* gene loci leads to expression of N-terminally truncated CTNNA1 and CTNNA2 isoforms

Martin Kask [1], Priit Pruunsild [1], Tõnis Timmusk *

Tallinn University of Technology, Department of Gene Technology, Akadeemia tee 15, Tallinn 12618, Harjumaa, Estonia

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ABSTRACT

α-Catenins (CTNNAs) are essential for the regulation of cell–cell and cell–matrix interactions in tissues. All human *CTNNA* genes contain antisense oriented leucine rich repeat transmembrane (*LRRTM*) genes within their seventh introns. Recently, a haplotype upstream of one of the human *LRRTM* genes, *LRRTM1* that resides in *CTNNA2*, was shown to be associated with handedness and schizophrenia. Here, we show that both *CTNNA1* and *CTNNA2* contain alternative 5′ exons linked to bidirectional promoters that are shared with the antisense oriented *LRRTM2* and *LRRTM1* genes, respectively. We demonstrate that bidirectional activity of these promoters results in alternative *CTNNA1* and *CTNNA2* transcripts that are expressed at high levels in the nervous system and show that N-terminally truncated CTNNA1 and CTNNA2 proteins lacking the β-catenin interaction domain are produced from these alternative *CTNNA* mRNAs. In addition, our results indicate that the haplotype that affects *LRRTM1* expression and is associated with schizophrenia and handedness, could also influence the expression of brain-enriched alternative transcripts of *CTNNA2*.

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1. Introduction

α-Catenins are involved in formation and maintenance of structural integrity of tissues by mediating cell–cell and cell–matrix interactions through coupling cadherin–β-catenin complexes to the cytoskeleton [1]. α-Catenins bind strongly either to the cadherin–β-catenin complex or actin, regulate actin filament assembly and control the dynamics of cadherin-dependent junctions [2,3].

In mammals there are three subtypes of α-catenins: αE-catenin (CTNNA1), expressed predominantly in non-neural tissues [4], αN-Catenin (CTNNA2), expressed widely in the central nervous system [5], and αT-catenin (CTNNA3), expressed primarily in the testis and heart [6]. Variability in α-catenin protein isoforms is generated by alternative splicing. Alternative mRNAs of *CTNNA1* or *CTNNA2* encode a C-terminally truncated isoform of αE-catenin [7] or an isoform of αN-catenin with in-frame insertion in the C-terminal region [8], respectively. In addition, transcripts of *CTNNA2* and *CTNNA3* that contain an alternative 5′ exon instead of the conventional initial exon encode isoforms with truncated N-termini [9,10]. With the exception of testis-specific N-terminally truncated CTNNA3 isoform that does not bind β-catenin [10], the functional significance of alternative α-catenin isoforms is unknown.

The *CTNNA1*, *CTNNA2* and *CTNNA3* genes contain antisense oriented leucine rich repeat transmembrane (*LRRTM) 2*, *LRRTM1* and *LRRTM3* genes, correspondingly, within their seventh intron [11]. The *LRRTM* genes encode transmembrane proteins that regulate presynaptic differentiation [12]. Importantly, *LRRTM1* has been associated with establishment of handedness and susceptibility to schizophrenia because of a specific haplotype upstream of *LRRTM1* [13]. However, it has not been thoroughly addressed whether the regulatory effect accompanied by this haplotype on *LRRTM1* expression, affects expression of *CTNNA2*. Here, we show that human *CTNNA1* and *CTNNA2* share bidirectional promoters with *LRRTM2* and *LRRTM1*, respectively, leading to the expression of N-terminally truncated CTNNA1 and CTNNA2 isoforms.

2. Materials and methods

All experiments with human tissues and all animal procedures were approved by the local ethics committee. Bioinformatic analysis, RNA isolation, mRNA expression analyses by RT-PCR, rapid amplification of cDNA 5′ ends (5′ RACE), RNase protection assay (RPA), cloning of cDNAs encoding full-length proteins, cell culture, DNA transfection, luciferase reporter assay, Western blotting and immunocytochemistry were performed according to standard procedures. Detailed description of materials and methods, including primers and antibodies, is provided in the Supplementary materials and methods.

* Corresponding author. Fax: +372 6204400.
E-mail address: tonis.timmusk@ttu.ee (T. Timmusk).
[1] These authors contributed equally to this work.

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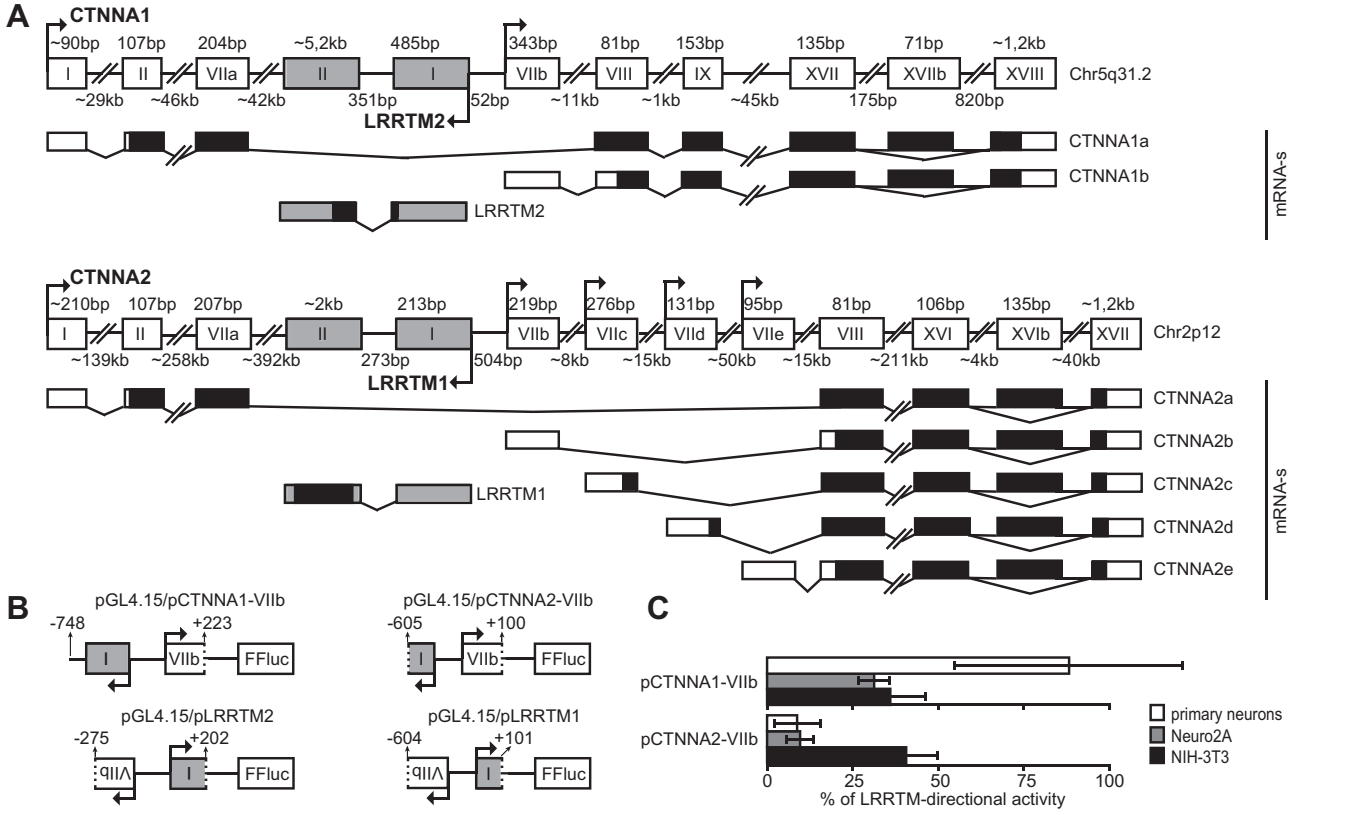

Fig. 1. Genomic structures of human *CTNNA1*/*LRRTM2* and *CTNNA2*/*LRRTM1* gene loci and bidirectional activities of the *CTNNA1*-VIIb/*LRRTM2* and *CTNNA2*-VIIb/*LRRTM1* promoters. (A) Structural organization of human *CTNNA1*, *LRRTM2*, *CTNNA2* and *LRRTM1* exons and introns was determined by analyzing genomic and mRNA sequence data using bioinformatics and RT-PCR. White and gray boxes represent *CTNNA* and *LRRTM* exons, respectively. Black lines represent introns. The orientation of transcription is shown by arrows. Arabic numerals above the exons and below the introns indicate their sizes. Exon numbers are shown in roman characters. White and gray boxes of mRNAs represent non-coding regions of exons. Black boxes designate translated regions of exons. (B) FFluc reporter constructs used for determining the bidirectional activity of the *CTNNA1*-VIIb/*LRRTM2* and *CTNNA2*-VIIb/*LRRTM1* promoters. Construct names indicate the direction of promoter activity analyzed. Numbers indicate the lengths of the cloned promoters in bps relative to the most 5′ TSS on the sense strand. (C) Promoters in front of *CTNNA1* exon VIIb and *CTNNA2* exon VIIb activate transcription bidirectionally. Percent of *LRRTM2*- and *LRRTM1*-directional promoter activity, respectively, is shown in rat primary cultured cortical neurons, Neuro2A neuroblastoma and NIH-3T3 fibroblast cells. Results of two independent experiments measured in triplicates and normalized to thymidine kinase (TK) promoter-dependent renilla luciferase (Rluc) signals derived from cotransfected TK-Rluc constructs are shown. Error bars represent SD.

3. Results

3.1. Identification of novel alternative 5′ exons of human CTNNA1 and CTNNA2 genes

Using bioinformatics we identified novel potential alternative 5′ exons in the seventh intron of both human *CTNNA1* and *CTNNA2*. In *CTNNA1* there is one such exon that we have named exon VIIb (Fig. 1A). In *CTNNA*2 we identified four potential 5′ exons in the seventh intron that are named here VIIb, VIIc, VIId and VIIe (Fig. 1A). Hereafter the conventional full-length *CTNNA* transcripts are referred to as *CTNNA1a* and *CTNNA2a*. Transcripts containing the novel 5′ exons are named according to the designation of the alternative seventh exon: *CTNNA1b* and *CTNNA2b*, *CTNNA2c*, *CTNNA2d* or *CTNNA2e* (Fig. 1A, GenBank IDs: HQ589335, HQ589336, BX537769, DC331874 and DC340948, respectively). Exon VIIb of *CTNNA1* and exon VIIb of *CTNNA2* are located in head-to-head orientation with antisense oriented *LRRTM2* and *LRRTM1* gene, respectively, and could share a common bidirectional promoter with the corresponding *LRRTM*. In order to support this hypothesis and to verify that these exons are used as 5′ exons, we applied the 5′ RACE method. We used human hippocampal cDNA and primers targeting exon IX of *CTNNA1* or *CTNNA2* and the 5′ exon of *LRRTM2* or *LRRTM1*. Firstly, our results showed that exon VIIb of *CTNNA1* has at least 11 different transcription start sites (TSSs) spanning 271 bp (Supplementary Fig. 1). We detected two TSSs separated by 28 bp for *LRRTM2* and found that the distance between the most 5′ TSS of *CTNNA1* exon VIIb and the most 5′ TSS of *LRRTM2* is only 52 bp (Supplementary Fig. 1). Secondly, we found that usage of only two of the four *CTNNA2* alternative seventh exons is detectable in the human hippocampus. With *CTNNA2* RACE primers the obtained clones contained predominantly exon VIIb of *CTNNA2* and on rare occasions usage of exon VIId was detected. None of the RACE clones comprised *CTNNA2* exon VIIc or VIIe, indicating that transcription of these exons is infrequent and below the detection limit of our assay. *CTNNA2* exon VIIb has at least five TSSs spanning 16 bp and *LRRTM1* has two TSSs that are 4 bp apart (Supplementary Fig. 1). The distance between the most 5′ TSS of *CTNNA2* exon VIIb and the most 5′ TSS of *LRRTM1* is 504 bp. For *CTNNA2* exon VIId we mapped two adjacent nucleotides as TSSs (Supplementary Fig. 1). Collectively, these results corroborated that *CTNNA1* exon VIIb and *CTNNA2* exon VIIb and VIId are used as initial exons and transcribed into *CTNNA* mRNAs that lack exons I-VIIa.

3.2. Bidirectional activities of CTNNA1-VIIb/LRRTM2 and CTNNA2-VIIb/LRRTM1 promoters

We used luciferase reporter assay to analyze transcription-promoting activities of the putative bidirectional promoters of *CTNNA1* exon VIIb and *LRRTM2* (*CTNNA1*-VIIb/*LRRTM2*) and of *CTNNA2* exon VIIb and *LRRTM1* (*CTNNA2*-VIIb/*LRRTM1*), respectively. We transfected mouse fibroblast NIH-3T3 and neuroblastoma Neuro2A cells

and rat primary cortical neurons with constructs containing these promoter regions in front of the firefly luciferase (FFluc) reporter gene (Fig. 1B and Supplementary Fig. 1) and determined their ability to promote transcription in both orientations. Overall, the results showed that the cloned genomic sequences activated transcription in both directions, whereas the strengths of the promoters were greater in the direction of *LRRTM* genes (Fig. 1C). *CTNNA1*-VIIb/*LRRTM2* promoter activity in the direction of *CTNNA1* was 88%, 29% and 31% of *LRRTM2*-directional activity in primary neurons, Neuro2A and NIH-3T3 cells, respectively (Fig. 1C). The corresponding results for the *CTNNA2*-VIIb/*LRRTM1* promoter were 9%, 10% and 40% (Fig. 1C). Altogether, the results of these experiments demonstrate that the genomic regions spanning the TSSs of *CTNNA1* exon VIIb and *LRRTM2* or *CTNNA2* exon VIIb and *LRRTM1* contain bidirectional promoters that have cell type- and orientation-specific regulatory features and in general are stronger in the direction of the *LRRTM* genes.

3.3. Expression of CTNNA1 and CTNNA2 alternative transcripts

To describe the expression patterns of *CTNNA1* and *CTNNA2* alternative transcripts in human tissues we performed RT-PCR with transcript-specific primers that amplify either the conventional 5′ exon containing mRNAs (*CTNNA1a* or *CTNNA2a*) or mRNAs containing the novel exon VIIb as the initial exon (*CTNNA1b* or *CTNNA2b*). In the case of *CTNNA2* we concentrated on novel exon VIIb containing transcripts and not on other alternative exon VII containing mRNAs because our RACE experiments showed no detectable usage of exon VIIc and VIIe and our RT-PCR analysis did not show any expression of *CTNNA2* exon VIId in human brain (data not shown). The RT-PCR experiments showed that expression levels of *CTNNA1a* were relatively invariable among the tissues analyzed, whereas *CTNNA2a* was expressed at different levels in almost all tissues and was barely detectable or not expressed only in the lung, placenta and thymus (Fig. 2A). The novel transcripts *CTNNA1b* and *CTNNA2b* had considerable bias for higher expression levels in the nervous system. *CTNNA1b* was strongly expressed in the brain and cerebellum, moderately in the placenta, liver and lung and weakly expressed or not detectable in other tissues analyzed (Fig. 2A). *CTNNA2b* was expressed very strongly only in the brain and was detectable at significantly lower levels in the cerebellum and liver. Next we analyzed *CTNNA1* and *CTNNA2* mRNA expression in human brain. Our results revealed that except higher levels in the corpus callosum and dorsal pons, *CTNNA1a* was expressed at similar levels in most brain regions analyzed (Fig. 2B). The novel *CTNNA1b* transcripts were expressed in all brain regions with considerably higher expression levels in the frontal and occipital lobe, corpus mammilare and cerebellum. *CTNNA2a* and *CTNNA2b* had partially overlapping but clearly different expression patterns in the brain. *CTNNA2a* was expressed in all brain regions analyzed with higher levels in the olfactory tract, frontal lobe, infundibulum, cerebellum, ventral pons and caudate nucleus. *CTNNA2b* showed very high expression levels in the olfactory bulb, frontal, occipital and parietal cortex, infundibulum, corpus mammilare, dorsal medulla, hippocampus, amygdala, thalamus and pineal gland, and was expressed at lower levels in several other brain regions (Fig. 2B).

Next we analyzed the relative expression levels of *CTNNA1b* and *CTNNA2b* transcripts compared to *CTNNA1a* and *CTNNA2a*, respectively, in human brain. We used RPA to address this question and the results showed that transcripts containing the novel 5′ exons were expressed at lower levels compared to mRNAs containing

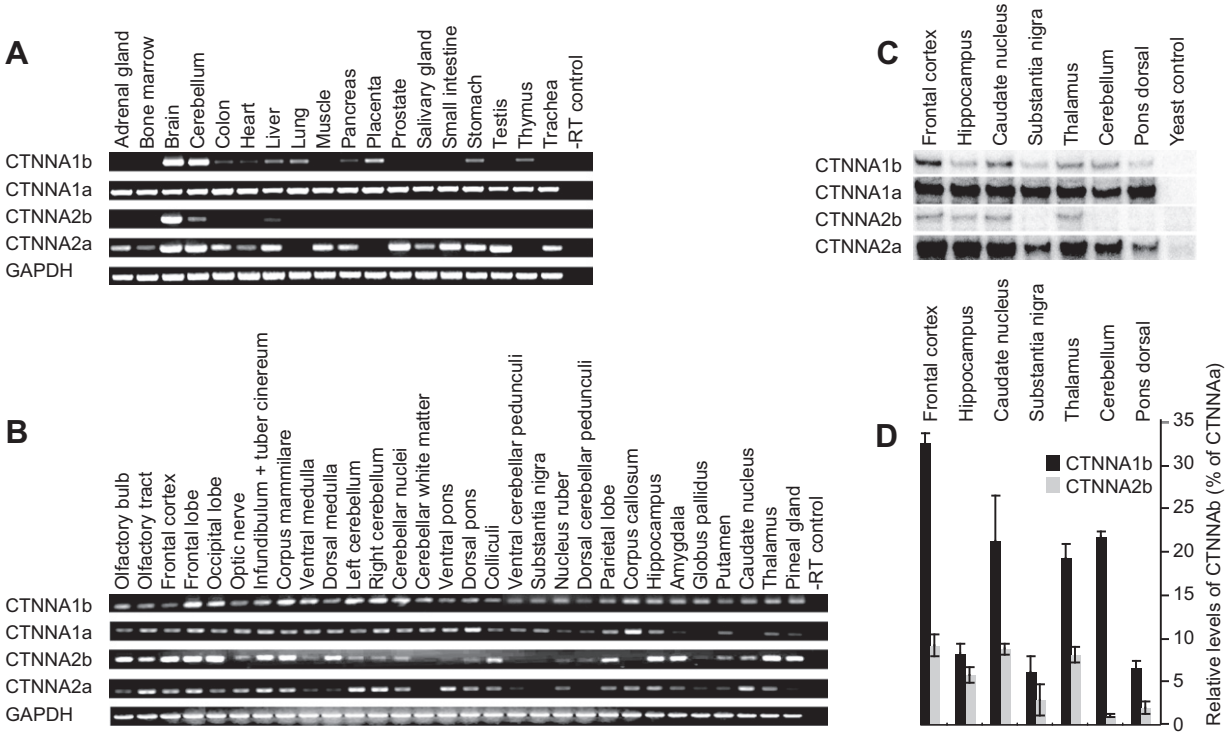

Fig. 2. Expression of alternative *CTNNA1* and *CTNNA2* transcripts in human tissues and brain regions. (A and B) Semiquantitative analysis of *CTNNA1b*, *CTNNA1a*, *CTNNA2b*, *CTNNA2a* and control *GAPDH* mRNA expression by RT-PCR in various human tissues (A) and brain regions (B). (C) Quantitative analysis of *CTNNA1b* and *CTNNA2b* mRNA levels relative to *CTNNA1a* and *CTNNA2a* transcript levels, correspondingly, by RPA in different human brain regions. The RPA probes spanned exons VIIb to exon XI in case of *CTNNA1* and exons VIIb to exon X in case of *CTNNA2*. A representative image of the results of two independent assays is shown. (D) Quantification of RPA data in C. Percent of *CTNNA1b* or *CTNNA2b* mRNA relative to the levels of *CTNNA1a* or *CTNNA2a* mRNA is shown. Results of two independent experiments are shown. Error bars represent SD. *CTNNA1b* and *CTNNA2b*, exon VIIb containing transcripts of *CTNNA1* and *CTNNA2*, respectively. *CTNNA1a* and *CTNNA2a*, full-length transcripts of *CTNNA1* and *CTNNA2*, respectively.

the conventional 5′ exons in all brain regions analyzed (Fig. 2C). *CTNNA1b* transcripts were approximately 3-fold, 5-fold or 10-fold less abundant than *CTNNA1a* mRNAs in frontal cortex and caudate nucleus, thalamus and cerebellum or hippocampus and substantia nigra, respectively, and constituted only about 5% of *CTNNA1a* levels in ventral medulla (Fig 2D). *CTNNA2b* was 10- to 15-fold less expressed than *CTNNA2a* in frontal cortex, hippocampus, caudate nucleus and thalamus and was barely detectable in other brain regions analyzed (Fig. 2D).

3.4. Expression of CTNNA1 and CTNNA2 protein isoforms

To determine whether the novel exon VIIb containing *CTNNA1* and *CTNNA2* transcripts result in expression of N-terminally truncated CTNNA1b (536 aa; predicted MW 59.6 kDa) and CTNNA2b (537 aa; predicted MW 59.9 kDa) proteins, correspondingly, we performed western blot analyses of CTNNA1 and CTNNA2 expression in human tissues and cancer cell lines with the anti-E-catenin (C-19) and anti-N-catenin (C-19) antibodies (abs). The anti-E-catenin (C-19) ab recognizes the C-termini of CTNNA1 and CTNNA2 and the anti-N-catenin (C-19) ab recognizes specifically the C-terminus of CTNNA2 (data not shown). The results with the anti-E-catenin (C-19) ab demonstrated that among the tissues analyzed, the full-length CTNNA1a and/or CTNNA2a was expressed at high levels in the cortex, hippocampus and cerebellum, at lower levels in the lung and liver and at very low levels in the muscle (Fig. 3A). Strong signal for the novel N-terminally truncated CTNNA1b and/or CTNNA2b was detected only in the cerebellum. The results with the anti-N-catenin (C-19) ab showed that the full-length CTNNA2a was expressed in the cortex, hippocampus, cerebellum and testis (Fig. 3A). The expression of the novel N-terminally truncated CTNNA2b was not detected with this ab indicating that the shorter isoform observed with the anti-E-catenin (C-19) ab was CTNNA1b (Fig. 3A). Notably, immunoreactivity at higher molecular weight than expected for CTNNA2a was additionally detected with the anti-N-catenin (C-19) ab in human brain samples, especially strongly in the cerebellum (Fig. 3A), but the identity of this signal is unknown. In all human cancer cell lines analyzed with the anti-E-catenin (C-19) ab we detected expression of CTNNA1a and/or CTNNA2a (Fig. 3B). Also, in all cell lines analyzed, except in the human colon adenocarcinoma LoVo cells, low levels of the shorter isoform CTNNA1b and/or CTNNA2b were present. With the anti-N-catenin (C-19) ab we detected relatively high level of CTNNA2a expression in the melanoma SK-Mel and cervical cancer HeLa cells, whereas weak expression was observed in all but LoVo cells (Fig. 3B). The novel N-terminally truncated CTNNA2b isoform was expressed in SK-Mel cells as evidenced from the results with the anti-N-catenin (C-19) ab. Collectively, these data illustrate that in addition to the full-length CTNNA proteins, the N-terminally truncated CTNNA1b and CTNNA2b are expressed in several human cancer cell lines and CTNNA1b is expressed in the human cerebellum.

Finally, we analyzed the subcellular localization of the novel CTNNA1 and CTNNA2 isoforms. We used overexpression of V5 epitope-tagged CTNNA1b or CTNNA2b in NIH-3T3 cells followed by immunocytochemistry with the anti-V5 ab. Clear localization of both CTNNA1b-V5 and CTNNA2b-V5 in the cytoplasm in proximity of the cell membrane was detected (Fig. 3C), indicating that these CTNNA1 and CTNNA2 isoforms are suitable for regulating cell-cell and cell-matrix interactions.

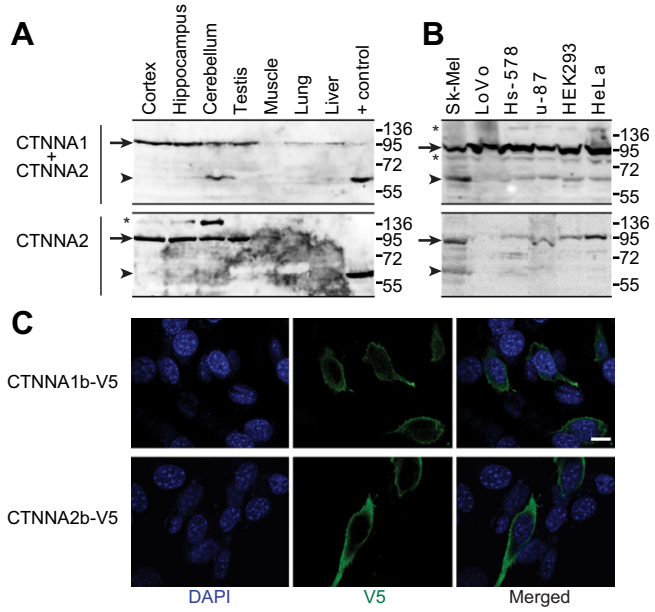

Fig. 3. Expression of CTNNA1 and CTNNA2 proteins in various human tissues and cell lines and subcellular localization of CTNNA1b-V5 and CTNNA2b-V5 proteins in NIH-3T3 cells. (A and B) Western blot analysis of CTNNA1 and CTNNA2 expression in human tissues (A) and cell lines (B). Human CTNNA1 and CTNNA2 were detected with anti-E-catenin (C-19) ab and human CTNNA2 was detected with anti-N-catenin (C-19) ab. Arrow, CTNNA1a and/or CTNNA2a; arrowheads, CTNNA1b and/or CTNNA2b; + control, human CTNNA1b (upper panel) or human CTNNA2b (lower panel) overexpressed in NIH-3T3 cells. Sk-Mel, human melanoma cells; LoVo, human colorectal adenocarcinoma cells; Hs-578, human breast carcinoma cells; u-87, human glioma cells, HEK293, human embryonic kidney cells; and HeLa, human cervical carcinoma cells. Asterisks mark unidentified immunoreactivity. Protein sizes are given in kDa. (C) Subcellular localization of CTNNA1b-V5 and CTNNA2b-V5 proteins in NIH-3T3 cells. NIH-3T3 cells overexpressing CTNNA1b-V5 or CTNNA2b-V5 were immunostained with anti-V5 ab. DAPI was used to visualize cell nuclei. Scale bar is 10 μm.

4. Discussion

In this study we have identified alternative 5′ exons in human *CTNNA1* and *CTNNA2* that share bidirectional promoters with antisense oriented nested genes *LRRTM2* or *LRRTM1*, respectively. We show that the novel 5′ exon VIIb containing *CTNNA1* transcripts are expressed in the nervous system at higher levels than in other tissues and that the novel 5′ exon VIIb containing *CTNNA2* mRNAs are expressed almost exclusively in the nervous system. These expression patterns resemble those of *LRRTM2* and *LRRTM1*, correspondingly [11]. This suggests that the promoters of the head-to-head located 5′ exons are regulated as single functional units in both directions similarly to a significant proportion of mammalian genes with bidirectional promoters [14]. On the other hand, we observed that the direction-specific strength of the *CTNNA1*-VIIb/*LRRTM2* and *CTNNA2*-VIIb/*LRRTM1* promoters is regulated in a cell type-dependent manner because we detected variation in the ratio of *CTNNA*-directional activity relative to *LRRTM*-directional activity in different cells for both promoters. Thus, although the location of the *LRRTM* genes inside the *CTNNA*s might have forced usage of cryptic *CTNNA* VIIb exons as alternative initial exons resulting in co-ordinately regulated transcripts, orientation-specific differences in the regulation of these promoters in different cells could reflect that functionally significant roles may have evolved for usage of the promoters in both orientations.

A specific haplotype upstream of *LRRTM1* has been demonstrated to be associated with schizophrenia and handedness when inherited paternally [13] and, importantly, an independent study has provided support for this finding [15]. Interestingly, while *LRRTM1* was shown to be imprinted, the *CTNNA2* gene that harbors *LRRTM1*, was found not to be affected [13]. However, the method that was used to analyze *CTNNA2* expression in the study by Francks et al. did not discriminate between the *CTNNA2a* and *CTNNA2b* transcripts. Our results showing that *CTNNA2b* and *LRRTM1* share a

bidirectional promoter raise the possibility that similarly to *LRRTM1* the novel *CTNNA2b* is regulated by imprinting and is associated with the development of schizophrenia. We controlled this hypothesis by analyzing monoallelic expression of *CTNNA2b* in five post-mortem brain samples, but our results showed biallelic expression of *CTNNA2b* in all of them (data not shown). Nevertheless, imprinting of *CTNNA2b* cannot be ruled out because imprinting of *LRRTM1* has been shown only in a subset of human samples [13]. Therefore, more extensive analysis of *CTNNA2b* allelic expression in human samples where *LRRTM1* is imprinted would be necessary to explore the possible link between *CTNNA2* and schizophrenia or handedness in future studies, especially in the light of the knowledge that CTNNA2 regulates the structure of synaptic contacts [16] and is essential for normal brain development [17].

According to our western blot analysis the novel N-terminally truncated CTNNA1b protein isoform is expressed at a comparable level with the full-length CTNNA1a in the adult human cerebellum, but is barely detectable in other tissues analyzed. Expression of the N-terminally truncated CTNNA2b, however, was below the detection limit in human tissue samples, including in cerebral cortex and hippocampus, where we recorded relatively high mRNA levels of the respective transcript. Interestingly, Mexal et al. have reported expression of an approximately 65 kDa CTNNA2 isoform in the human hippocampus with the same ab as used in this study [9], suggesting that, in principle, there is an N-terminally truncated CTNNA2 isoform expressed in the human brain, but its expression levels could vary between individuals. Mexal et al. claim that the shorter isoform results from translation of a *CTNNA2* transcript that contains VIIc as the 5′ exon (GenBank ID: BX537769). Our results suggest that it is more likely that the approximately 65 kDa CTNNA2 isoform detected by Mexal et al. results from mRNAs containing the *CTNNA2* exon VIIb as the 5′ exon instead, because our RACE experiments with primers specific for the ninth exon of *CTNNA2* resulted predominantly in RACE clones containing exon VIIb and on rare occasions also exon VIId but not exon VIIc. In addition, whereas there is only one EST containing the 5′ exon described by Mexal et al. available in the databases, ESTs containing exon VIIb are much more abundant. These data suggest that the alternative exon VIIb, which is head-to-head with *LRRTM1*, is used more frequently than the other alternative seventh exons, although usage of the latter in specific circumstances cannot be excluded. Nevertheless, determining which of the alternative *CTNNA2* mRNAs are used for protein production in human brain *in vivo* is important because translation of exon VIIb and VIIe containing transcripts would result in simple truncation of the N-terminus of *CTNNA2* due to lack of an in-frame translation start codon in the corresponding exon, but translation of exon VIIc or VIId containing transcripts potentially results in 31 or 17 unique N-terminal amino acids in the CTNNA2 protein, respectively (Supplementary Fig. 2).

The function of the N-terminally truncated CTNNA1 and CTNNA2 has yet to be elucidated. Nonetheless, data available for the full-length CTNNAs enable several conclusions to be drawn. For example, dimerization of CTNNAs through the N-terminal domains has been described [18]. The novel CTNNA protein isoforms do not contain this domain and therefore most probably do not dimerize. Due to the fact that monomeric CTNNA has been shown not to compete with Arp2/3 complex for binding actin [2], novel isoforms potentially lack the ability to inhibit branching of actin filaments. Also, novel isoforms of CTNNA could be deficient in connecting the cadherin-β-catenin complex to actin cytoskeleton because they lack the N-terminal β-catenin binding region [19]. Thus, it is possible that the ratio between expression levels of the full-length and N-terminally truncated CTNNA isoforms is important for dynamic regulation of cadherin-dependent adhesion. It can be further speculated that higher levels of the truncated isoform are needed for the regulation of cell–cell contacts in the nervous system as both *CTNNA1* and *CTNNA2* exon VIIb containing transcripts were shown here to be more abundant in the brain than in other tissues and high level of N-terminally truncated CTNNA1 protein expression was detected in human cerebellum and not in other tissues analyzed. Additionally, as we observed expression of N-terminally truncated CTNNA1 and CTNNA2 in several human cancer cell lines, it could be argued that disruption of the ratio between the short to the full-length CTNNA protein might contribute to or be indicative of cancerous phenotype. Further research is needed to support these assumptions, though.

In conclusion, this work shows that alternative 5′ exon VIIb containing mRNAs of human *CTNNA1* and *CTNNA2* genes are transcribed under the control of bidirectional promoters shared with *LRRTM2* and *LRRTM1*, respectively. These novel *CTNNA* transcripts have a considerable bias for higher expression levels in the central nervous system, indicating to a possible brain-specific role for the resulting N-terminally truncated α-catenins.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2011.06.085.

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