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## Nicotinic receptors as SARS-CoV-2 Spike co-receptors?

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1 **Abstract:** Nicotinic acetylcholine receptors (nAChRs) play an important role in homeostasis  
2 and respiratory diseases. Controversies regarding the association between COVID-19  
3 hospitalizations and smoking suggest that nAChRs may contribute to SARS-CoV-2 respiratory  
4 syndrome. We recently detailed the expression and localization of all nAChR subunits in the  
5 human lung. Since virus association with nAChRs has been shown in the past, we  
6 hypothesize that nAChR subunits act as SARS-CoV-2 Spike co-receptors. Based on sequence  
7 alignment analysis, we report domains of high molecular similarities in nAChRs with the  
8 binding domain of hACE2 for SARS-CoV-2 Spike protein. This hypothesis supported by *in*  
9 *silico* pilot data provides a rational for the modelling and the *in vitro* experimental validation  
10 of the interaction between SARS-CoV-2 and the nAChRs.

11 **Keywords:** Nicotinic receptors; COVID-19; SARS-CoV-2; hACE2; lung

12

13

## 14 **Background**

15 Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is responsible for the global  
16 pandemic of coronavirus disease 2019 (COVID-19) [1,2]. Understanding its structure and  
17 molecular interactors are crucial to explain the transmission, viral infection, and replication  
18 [3]. Recent controversies regarding the impact of smoking on COVID-19 pointed to the  
19 potential role of nicotinic acetylcholine receptors (nAChRs) in human angiotensin converting  
20 enzyme-2 (hACE2) interaction with SARS-CoV-2 [4,5]. A similar convergence was established  
21 regarding the association of nAChRs with rabies virus where the binding was ultimately  
22 experimentally demonstrated a few decades ago [6–10].

23 Since it has been proposed that nAChRs may play a key role in the SARS-CoV-2-mediated  
24 inflammatory syndrome [11,12], additional avenues are currently explored considering that:  
25 (i) nAChRs are widely expressed in organs targeted by the virus including lung, nose, brain,  
26 gastrointestinal tract, liver, and smooth muscles [13,14]; (ii) nAChRs are also present on  
27 endothelial and platelet cells [15] while altered endothelial function induces vascular  
28 thrombosis and microangiopathy in COVID-19 [16,17]; (iii) nAChRs are involved in  
29 angiogenesis and arterial diseases [18], while significant vascular angiogenesis was found in  
30 lungs from patients who died from COVID-19 [19].

31

## 32 **The hypothesis**

33 It was recently suggested that smoking may promote cellular uptake mechanisms of SARS-  
34 CoV-2 through CHRNA7 signalling [20], and subsequently, CHRNA7 transcripts were  
35 correlated with hACE2 levels [21], feeding the possible connections between hACE2 and  
36 nAChR localizations in airway epithelial cells. In addition, *in silico* analysis of nAChR ligands  
37 suggested an interaction between SARS-CoV-2 and nAChRs [22–24], while nicotine exposure  
38 may facilitate SARS-CoV-2 infection *in vitro* [25]. Nicotinic receptors are ligand-gated ion  
39 channels consisting of 5 membrane-spanning subunits selected from 16 proteins (CHRNA1-  
40 A7, A9-A10, B1-B4, D, E, G) that all harbour at least one extracellular domain of  
41 approximately 200 residues. Going one step further, we suggest that nAChRs may bind to  
42 SARS-CoV-2-RBD (Receptor Binding Domain) similar to hACE2 and potentially act as co-  
43 receptors for SARS-CoV-2-RBD at least in the airways where we documented the complete  
44 atlas of pulmonary nAChR subunits in terms of transcript expression and protein localization  
45 [26]. Transcripts of all 16 subunits were detected in airway epithelial cells or whole lung

46 tissues and only subunits  $\alpha 1/\alpha 2/\alpha 4/\beta 3/\gamma$  were not observed via immunofluorescent  
47 stainings performed on formalin-fixed paraffin-embedded lung tissues.

48

#### 49 **Empirical data**

50 The N-terminal domain of hACE2 binding to the spike (S) glycoprotein SARS-CoV-2-RBD and  
51 SARS-CoV-1-RBD has been characterized recently [27–30]. Twenty-four hACE2 residues were  
52 shown to interact with 21 SARS-CoV-2-RBD residues (region K417 to Y505) and 18 SARS-CoV-  
53 1-RBD residues (region R426 to Y491) organized in 4 motifs on hACE2 (**Figure 1A and B**).

54 Postulating that nAChRs may contain extracellular hACE2-like regions mimicking their  
55 interactions with SARS-CoV-2, and since structural data of the 16 nAChR subunits are  
56 incomplete, we performed bioinformatics analysis using the Clustal Omega program  
57 (Uniprot) to align each of the 16 nAChR subunits' extracellular topological domain protein  
58 sequences with the 4 motifs containing the binding residues of hACE2 with SARS-CoV-1 and  
59 2. We identified identical residues in the 4 regions of interests (ROI) as well as conservations  
60 between groups of similar properties with a particular focus on residues located within van  
61 der Waals (vdw) contact distance between the viral ligand and the receptor (24 red residues,  
62 **Figure 1 and Figure 2**).

63 Key residues to form a solid network between hACE2 and SARS-CoV-2-RBD are localized in  
64 the motif-1 (S19-Q42) and the motif-4 (K355-R357). The last residue (R393) was not included  
65 in the analysis since it was not in the proximity of other key residues involved in complex  
66 formation (**Figure 1**). Interestingly, CHRNA2/A4/A6/A7/A10/B1 presented no overlaps for  
67 the 4 motifs (**Figure 2 and Table 1**).

68 We established a score based on the percentage of matching residues either in the entire  
69 proposed binding region or solely considering the residues involved in vdw contacts (**Table**  
70 **1**). Each of the nAChR subunits presented on average 68.5% ([59.1-81.8]) of resemblance  
71 with hACE2 binding regions to SARS-CoV-2-RBD and 64.4% ([47.8-73.9]) solely taking into  
72 account vdw contacts. The best scores for the 2 parameters were obtained by CHRNA6  
73 (61.4%/73.9%), and CHRNB1 (81.8%/69.5%) (**Figure 2 and Table 1**). Most of nAChRs  
74 possessed mutations in the possible binding domains where a loss or a strong inhibition of

75 the interaction with SARS-CoV-1 and 2 was reported (**Table 1, [31]**). Mutagenesis might  
76 favour a beneficial role of nAChRs if they were found to bind SARS-CoV-2 but their levels of  
77 expression and specific localizations in various tissues weigh up the pros and cons in a  
78 complex and not fully elucidated biological scale.

## 79 **Consequences of the hypothesis and discussion**

80 Although these findings do not demonstrate that nAChRs can function as co-receptors for  
81 the ligand SARS-CoV-2-RBD, here we report a significant molecular similarity between hACE2  
82 binding sites and extracellular domains of nAChRs. Structural biology to match protein  
83 structures in 3D would ideally complement this bioinformatics analysis but crystallized  
84 structures of all human nAChR subunits are currently not fully resolved. Notably, the protein  
85 folding of nAChRs subunit should reveal the critical residues to allow the interaction with  
86 SARS-CoV-2-RBD. In addition, nAChRs function as pentamers, the complexity of the  
87 composition of the channel may also contribute to the potential interaction between SARS-  
88 CoV-2 and one of the subunits where binding would be possible. Interestingly, CHRNA6 and  
89 CHRNB1 transcripts were highly expressed in lung tissues and small airway epithelial cells,  
90 and the proteins were strongly detected in bronchi strengthening the possibility of the direct  
91 interaction between nAChR subunits and SARS-CoV-2 [26].

92 Although we focus here on similarities of a potential binding domain with hACE2, we do not  
93 exclude the possibility that SARS-CoV-2 may interact with alternative domains on nAChRs.  
94 The hypothesis of SARS-CoV-2 binding to nAChRs was originally based on the identification  
95 of similar known nAChR antagonist/agonist motif sequences on SARS-CoV-2 spike protein.  
96 This possible interaction has been sparsely discussed *in silico* [22,23,32]. Finally, although  
97 several pentamers are functionally characterized in the nervous system or muscles, the  
98 association of subunits in the airways is only partially elucidated and requires further  
99 investigations in the context of COVID-19 [26]. Conversely, nAChRs may play a role in COVID-  
100 19 progression beyond the respiratory system including systemic inflammation and the  
101 nervous system.

102 The modulation of nAChRs in the lung may increase pro-inflammatory cytokine production, a  
103 process potentially leading to the "cytokine storm" during infection [33,34]. Moreover,  $\alpha 7$   
104 nAChR has been involved in the control of inflammation associated with influenza virus

105 infection [35]. nAChR can also control COVID-19 physiopathology by modulating the Renin-  
106 Angiotensin System (RAS) [36]. This nicotine-induced imbalance of the two arms of the RAS  
107 is likely responsible for cardio-vascular dysfunction, and acute/chronic lung diseases  
108 associated with severe forms of COVID-19.

109 The potential neurotropism of SARS-CoV-2 has been discussed extensively. SARS-CoV-2 has  
110 been identified in the brain of patients [37]. There is by now a substantial amount of  
111 literature, and cases, that link neurological and psychiatric sequelae of COVID-19 to an  
112 implication of the human brain. The current state of the discussion has been reviewed [38].  
113 Of specific interest is a recent description of a case of Parkinson's Disease directly linked to  
114 the infection [39]. The working hypothesis is that SARS-CoV-2 infection can be a "trigger"  
115 precipitating the onset of neuropathology. Nicotinic acetylcholine receptors (nAChRs) are  
116 important transmembrane neurotransmitter receptors for acetylcholine in the mammalian  
117 brain [40]. They modulate key neuronal functions such as excitability, synaptic transmission,  
118 and plasticity. They can change neuronal network states and consequently whole-brain  
119 responses to internal and external inputs and have been linked to disease [41]. They are also  
120 exogenously activated by nicotine and are responsible for the events leading to nicotine  
121 addiction [42]. The predominant receptors in the brain are  $\alpha 4\beta 2^*$  containing hetero-, and  
122  $(\alpha 7)_5$  homo-pentamers [43]. Being particularly expressed in the cortex, hippocampus, and  
123 dopaminergic reward system [44], these receptors are considered to be important drug  
124 targets [45]. The  $\alpha 6$  and  $\alpha 5$ -containing receptors are more restricted, but still very present in  
125 sub-cortical "modulatory" areas. The presence of SARS-CoV-2 in the brain parenchyma can  
126 therefore potentially interfere with higher cognitive function. nAChRs are potentially  
127 implicated in the penetration of SARS-CoV-2 into the central nervous system, as they are  
128 expressed in many nerve endings [46]. The olfactory route has been established in previous  
129 types of coronaviruses able to enter nerve endings and use retrograde axonal transport [47].  
130 A possibility is also the vagus nerve. It is well established that it contains most nAChR  
131 subunits [48].

132 According to each individual clinical context including but not limited to respiratory diseases  
133 and smoking history [49,50], nAChR binding to SARS-CoV-2-RBD may facilitate virus  
134 attachment to cell surface before virus entry, or serve as a decoy either harmful as it would  
135 prevent the binding of acetylcholine, or beneficial as it would dampen the virus load that

136 may infect epithelial cells [51]. Structural biology and functional analysis on SARS-CoV-2-RBD  
137 in complex with nAChRs subunits alone or as pentamers is required to resolve the possible  
138 interactions and unveil additional therapeutic strategies.

139

140



141 **Abbreviations**

142	ACE-2	Angiotensin converting enzyme-2
143	BR	Binding region
144	COVID-19	Coronavirus disease 2019
145	ETD	Extracellular topological domain
146	nAChRs	Nicotinic acetylcholine receptors
147	PDB	Protein data bank
148	RBD	Receptor binding domain
149	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
150	vdw	Van der Waals
151		

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321 **Figure Legends**

322 **Figure 1. hACE2 binding motifs to SARS-CoV-1 and 2 sequences.** (A) Localizations of motifs 1  
323 to 4 on hACE2 sequence (Q9BYF1) are highlighted in orange, blue, purple, and green  
324 respectively. Red residues are residues involved in van der Waals contact distance between  
325 hACE2 and SARS-CoV-1 and 2. Framed residues correspond to residues that are either  
326 interacting with SARS-CoV-2-RBD only (E35) or SARS-CoV-1-RBD only (Q325, E329). The  
327 residue highlighted in yellow corresponds to the 24th residue involved in van der Waals  
328 contact distance but not in the immediate proximity of other residues involved in the  
329 binding, therefore it was not included in the analysis. (B) The crystal structure (Protein Data  
330 Bank: 6M0J) shows the 4 motifs highlighted in (A) with similar colour codes. The crystal  
331 structure of SARS-CoV-2 spike receptor-binding domain bound with hACE2 (PDB ID: 6M0J  
332 [52]) was highlighted and exported from the viewer of the Research Collaboratory for  
333 Structural Bioinformatics (RCSB; [www.rcsb.org](http://www.rcsb.org)).

334

335 **Figure 2. Clustal alignment of nAChRs with hACE2 binding motifs.** Data from the UniProt  
336 Knowledgebase (UniProtKB, [53]) were used to perform a sequence alignment study of  
337 matching residues between hACE2/SARS-CoV-2 binding sites and nAChR protein sequences.  
338 The UniProtKB/Swiss-Prot accession numbers of the sequences used for analyzing the  
339 similarities are the following: ACE2 (Q9BYF1), CHRNA1 (P02708), CHRNA2 (Q15822), CHRNA3  
340 (P32297), CHRNA4 (P43681), CHRNA5 (P30532), CHRNA6 (Q15825), CHRNA7 (P36544),  
341 CHRNA9 (Q9UGM1), CHRNA10 (Q9GZZ6), CHRNB1 (P11230), CHRNB2 (P17787), CHRNB3  
342 (Q05901), CHRNB4 (P30926), CHRNG (P07510), CHRNE (Q04844), CHRND (Q07001). Motifs 1  
343 to 4 were aligned with the 16 nAChR sequences to identify molecular similarities. The nAChR  
344 extracellular topological domains' subunit sequences are represented with the partial  
345 alignment obtained with Clustal for the 4 motifs. \*, position with a single fully conserved  
346 residue; :, position with a residue showing conservation between groups of strongly similar  
347 properties (scoring >0.5 in the Gonnet PAM 250 matrix); ., position with a residue showing  
348 conservation between groups of weakly similar properties (scoring =<0.5 in the Gonnet PAM  
349 250 matrix).

350

351 **Table 1. Table presenting the sequence similarities with SARS-CoV-hACE2 binding motifs**  
 352 **for all nAChRs**

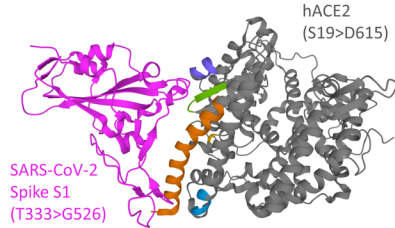
CHRN	ETDL	BRO	BR in ETD (44 R)			vdw contacts in ETD (23 R)			Mutagenesis
			Id (R, (%))	Sim (R, (%))	Tot (R, (%))	Id (R, (%))	Sim (R, (%))	Tot (R, (%))	
A1	21-255	Y	11 (25)	17 (38.6)	<b>28 (63.6)</b>	4 (17.4)	9 (39.1)	<b>13 (56.5)</b>	353 K>D 357 R>A
A2	27-264	N	14 (31.8)	16 (36.4)	<b>30 (68.2)</b>	5 (21.7)	8 (34.8)	<b>13 (56.5)</b>	353 K>D 357 R>A
A3	32-240	Y	12 (27.3)	20 (45.4)	<b>32 (72.7)</b>	6 (26.1)	10 (43.4)	<b>16 (69.5)</b>	31 K>D
A4	29-242	N	14 (31.8)	17 (38.6)	<b>31 (70.4)</b>	5 (21.7)	8 (34.8)	<b>13 (56.5)</b>	353 K>D 357 R>A
A5	23-254	Y	13 (29.6)	18 (40.9)	<b>31 (70.5)</b>	6 (26.1)	11 (47.8)	<b>17 (73.9)</b>	31 K>D 353 K>D
A6	26-239	N	16 (36.4)	11 (25)	<b>27 (61.4)</b>	9 (39.1)	8 (34.8)	<b>17 (73.9)</b>	
A7	23-230	N	12 (27.3)	14 (31.8)	<b>26 (59.1)</b>	5 (21.7)	9 (39.1)	<b>14 (60.8)</b>	
A9	26-237	Y	10 (22.7)	22 (50)	<b>32 (72.7)</b>	5 (21.7)	12 (52.2)	<b>17 (73.9)</b>	
A10	25-237	N	12 (27.3)	17 (38.6)	<b>29 (65.9)</b>	6 (26.1)	7 (30.4)	<b>13 (56.5)</b>	353 K>D 355 D>A
B1	24-244	N	16 (36.4)	20 (45.4)	<b>36 (81.8)</b>	6 (26.1)	10 (43.4)	<b>16 (69.5)</b>	353 K>D
B2	26-233	Y	15 (34.1)	16 (36.4)	<b>31 (70.5)</b>	7 (30.4)	9 (39.1)	<b>16 (69.5)</b>	
B3	25-232	Y	13 (29.6)	20 (45.4)	<b>33 (75)</b>	4 (17.4)	13 (56.5)	<b>17 (73.9)</b>	353 K>D
B4	22-236	Y	14 (31.8)	15 (34.1)	<b>29 (65.9)</b>	5 (21.7)	11 (47.8)	<b>16 (69.5)</b>	31 K>D
G	23-240	Y	14 (31.8)	14 (31.8)	<b>28 (63.6)</b>	5 (21.7)	7 (30.4)	<b>12 (52.1)</b>	353 K>D
E	21-239	Y	12 (27.3)	17 (38.6)	<b>29 (65.9)</b>	2 (8.7)	9 (39.1)	<b>11 (47.8)</b>	
D	22-245	Y	13 (29.6)	17 (38.6)	<b>30 (68.2)</b>	6 (26.1)	10 (43.4)	<b>16 (69.5)</b>	353 K>D

353 Highlighted nAChRs in grey present overlap in binding regions (BR) in Extracellular topological domains (ETD).  
 354 The binding regions correspond to the 4 motifs containing a total of 44 residues (R). The van der Waals (vdw)  
 355 contacts include 23 residues. ETDL, ETD position on protein sequence; BRO, BR overlaps; Id, fully conserved  
 356 residues (Number, % of total); Sim, residues with similar properties (Number, % of total); Tot, sums of the fully  
 357 conserved and similar residues (Number, % of total). Bold numbers indicate the best two hits. Mutagenesis  
 358 indicates the positions of the residues that were shown to be involved in a loss of SARS-CoV interaction and  
 359 that are also present on nAChR sequences.

360

**A**

	10	20	30	40	50
<b>motif1</b>	MSSSSWLLLS	LVAVTAAQ <b>ST</b>	IEE <b>QAKTFLD</b>	<b>KFNHE</b> AEDLF	<b>YQSSL</b> ASWNY
	60	70	80	90	100
<b>motif2</b>	NTNITEENVQ	NMNNAGDKWS	AFLKEQST <b>LA</b>	<b>QMY</b> PLQEIQN	LTVKLQLQAL
	310	320	330	340	350
<b>motif3</b>	AWDAQRIFKE	AEKFFVSVGL	PNMT <b>Q</b> GFW <b>EN</b>	SMLTDPGNVQ	KAVCHPTAWD
	360	370	380	390	400
<b>motif4</b>	LG <b>KGDFR</b> ILM	CTKVTMDDFL	TAHHEMGHIQ	YDMAYAAQPF	LL <b>R</b> NGANEGF

**B**



10 20 30 40 50  
 MRPWPLLLP SLCSAGLVV SEHETRLAK LFKDYSVVR PVEDHVVQ  
 60 70 80 90 100  
 VTVGLQLQL INVDVEVQV TTNVRLKGD **U** MVLFRPSCV TGLVPLFSLH  
 110 120 130 140 150  
 QNRWQVQV KRNFDYQVQV KKHIFSRKI WRFDLVNLN AGDFATVAFK  
 160 170 180 190 200  
 TKVLQYQTH IWTWPAIFK SYCEIIVTHF PFDQNCNSK LGTMVYDGSV  
 210 220 230 240 250  
 VAINPESQF DLGNMSESG VKWESRQWK HSVTYGQDF TPLDITVYHF  
 VMQRL

**CHRNA1**

10 20 30 40 50  
 MGSFCVPLFS FTKLISMLL LTPAGGERAK RFPFRAGDP LSSPSPALP  
 60 70 80 90 100  
 QGSHSTKED RLKPKLFRYSW NWRAPVPMVT SDVIVRSLQ SIAGLIDVDR  
 110 120 130 140 150  
 KNCMTTWW LKQESWDLK RWRPTFQSI TSLAVFESMI WIPFDVLYN  
 160 170 180 190 200  
 ADFEPAVQV TKAHLESTDT VHWVPAIFK SCSGIIITVF PFDQNCNSK  
 210 220 230 240 250  
 FQSMYDQAK IDLEQMGVQ DLKDWESGE MAAVNAVTA NSKDYDCAE  
 260 270 280 290 300  
 IYPTVATYAF IERL  
 \*\*\*

**CHRNA2**

10 20 30 40 50  
 MGSGLLPL ALSPPRLL LLLSLPVAR ASEARHLEF RLFEDVNEII  
 60 70 80 90 100  
 RPAVNSVDV IIEHFVMSQ LKRVDEVQI METNMLKQI WNDYKLNWP  
 110 120 130 140 150  
 SYGGASRQV VPACTWQDF VILYNAVQV FQVDFKRAL KYATGEVVI  
 160 170 180 190 200  
 PPAIFKQSK IDVTFPFDV QNCTMWSQV SYDAKAKLV LIGSMQVQ  
 210 220 230 240 250  
 YWESQWALI KAPYKHDIK YNCEIIVPD ITYSLYIRL  
 WYH **U** **U**  
 \*\*\*

**CHRNA3**

10 20 30 40 50  
 MGLGQGFAR LPLPLLLLL TGLLRASSHV ETRAHAERL LKLFQSYNK  
 60 70 80 90 100  
 KRFRVANSIS VVLVRFGLSI AGLIDVDEN CMHTTWWK QSHWYKLV  
 110 120 130 140 150  
 PDAFVYVSI IRPSELIRK PDIVLYNAD GDFATVAFK AHLFDGFR  
 160 170 180 190 200  
 MTPFAYSK CSIVITFFFV DQNCNTRKQ SWTYDQAKI LNMNSVQV  
 210 220 230 240 250  
 DLWMSGQWV IVDWVYNT RYKCEARLY PDITVAFVIR RL  
 WYH **U** **U**  
 \*\*\*

**CHRNA4**

10 20 30 40 50  
 MAARSGPRA LKLLLLQMD AGRCOLAGAA GGAORGLSEP SSIKHEHSL  
 60 70 80 90 100  
 LKQLPQYER WYRFVHLND KIKIKFGLT SQLVDVQEN QMHTNWLK  
 110 120 130 140 150  
 QEWIVKLR NFDQGGYIV IRVPSVDFV PDIVLFINAD GFEQSTSTK  
 160 170 180 190 200  
 VYRYWYVW TPFMAYNSC TIDVTFPD LQNCMSQV MYTSDYQSI  
 210 220 230 240 250  
 ILEDQVQD DFFISQEWI VSATQSKNR TQCCVYTV TYSYFIRKL  
 WYH **U** **U**  
 \*\*\*

**CHRNA5**

10 20 30 40 50  
 MLTSGQKGL HGLGLMLCV FTFPFGKGV CATEERLFK LFSHYQFIR  
 60 70 80 90 100  
 PVENSYVTF VHFVAITQL ANDEVQMI ETNMLSHIV NDKYLRWQV  
 110 120 130 140 150  
 EYDITIELV PAKIKKFDI VLYNAVQV QVQRTKALL KYNMILWTF  
 160 170 180 190 200  
 PAIFSSQK DITTFPFRH NCKLQSPV YKAEKIDLI LQSGVDFD  
 210 220 230 240 250  
 WNSQWELID ASDYKHDIK NCEIIVYDI TYSYFIRL  
 WYH **U** **U**  
 \*\*\*

**CHRNA6**

10 20 30 40 50  
 MRCSPQWVL ALAALLVVS LQGFQPKLY KELVYNPL ERFPANVQ  
 60 70 80 90 100  
 LTVFSLSL QIMQVDRQ VLTNVLWQV SWDHYLQWV VSEYGVYTF  
 110 120 130 140 150  
 RFPDQIQWF DILLNVAE RFDATHTV LWNVSQGV LPFQIFKSC  
 160 170 180 190 200  
 YLVDWFFPD VQWCKLFSV SYWQMSLQI QMGEADIS IPNGWELV  
 210 220 230 240 250  
 IPRSRSEY ECKQYFVW TFFVIMBT  
 WYH **U** **U**  
 \*\*\*

**CHRNA7**

10 20 30 40 50  
 MWSKCSIFP CMYFPAAR RAETAKDY AQKLNDFLE DYSNALVQ  
 60 70 80 90 100  
 DTVRYLQVI QITLQIQIM DERQULITAY IHTQYDQRA YLTKWQFD  
 110 120 130 140 150  
 SLDRITRSD LMRFDVLYI NKAQDSSEP WTVWVLYAD GLTWDAPI  
 160 170 180 190 200  
 TQSCCVVIT YFFPDQCN LTRQSYTYG KQVDFINALD SGLDSEID  
 210 220 230 240 250  
 VEWYRQMPA VHWVSYGCC SEYFVDTTF LLKRRS  
 WYH **U** **U**  
 \*\*\*

**CHRNA9**

10 20 30 40 50  
 MGLRSHLSL GLLLFLPLA ECLGAEGLA LKLFIRDLFAN YTSALRPVAD  
 60 70 80 90 100  
 TQDTNLVTE VLSQIIMD ERQVULYIV WIQEWDYAD LQWQRAYG  
 110 120 130 140 150  
 LDATRIFSL WRFVPIVYN KADAQFPGA STNVLRSGV AWSDAFAT  
 160 170 180 190 200  
 RSRCDVAAV FFDQAQGLQ FTSGMTHGG QLVDFRGA AASLADVENV  
 210 220 230 240 250  
 RWVLRQFAR RRVLTGQCC EYTFVYFVL LLRRAA  
 WYH **U** **U**  
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**CHRNA10**

10 20 30 40 50  
 MTFGLMLL GALGAPLQ VQSGAEKRL REKLFQSYDS SVRPAEVDV  
 60 70 80 90 100  
 RVRVSVLIL AGLISLNEK EMSTKYLVD LKMTDYLQV DPAHQDIDS  
 110 120 130 140 150  
 DRITASEYV FQVLLNND QNFVALDIS VVSDYDQVR WQFQYRS  
 160 170 180 190 200  
 CSIQYTFYF QWNTWTFPS SYDYSQV LQVLDQV QGHEIHBS  
 210 220 230 240 250  
 TFIENQWEI IHRFSLRQI PGIQDQSGR QROEYFILI IRK  
 WYH **U** **U**  
 \*\*\*

**CHRNA11**

10 20 30 40 50  
 MARQNPVAL LGLFLLRCL SGWWTQTE FLVSHLQFS RYNKLHPAT  
 60 70 80 90 100  
 NSESLVTVL MVSIAQLIV HREQIMTN VMLQSEMYI RLTKRFFPD  
 110 120 130 140 150  
 NNRVLRSLK HMLFVAVY NNAQYHVS FYNVAVSD QSLFMPAI  
 160 170 180 190 200  
 YSACKIEVY HFFPDQCT MFRSNTYDR TEIDLKSE VASLDITFS  
 210 220 230 240 250  
 QENDVALGK RRNENPDST YVDITDFLI IRK  
 WYH **U** **U**  
 \*\*\*

**CHRNA12**

10 20 30 40 50  
 MLPDMPLVL VLGIPSSAT GFNEIANDL ALRHLPQYI QRWVRFVH  
 60 70 80 90 100  
 NDFIKVPI KISLVQVDE KNGMTMWN LKQETKQL RANFDYQGI  
 110 120 130 140 150  
 HSLVSESL WLDIVLFRN ADRFREGSLM TKVYKSNQI WVMFPASK  
 160 170 180 190 200  
 SECTMVFY PFRQNCMSK FQSMYDQTM VDLILINQV DRKFFGSE  
 210 220 230 240 250  
 WEILNAKMK GNRQDGVSY FFITYSFLR RL  
 WYH **U** **U**  
 \*\*\*

**CHRNA13**

10 20 30 40 50  
 MRAPSLVLF FVALQDQNR CRVANAERK MDLNLKNTYI NNLIRPATS  
 60 70 80 90 100  
 SOLISIKQL SIQALIVNNE REQIMTNWV LQWETDYL TNSRSYGV  
 110 120 130 140 150  
 NILKPAKRI WLDVILVYN ADGTYEVYI VNLIVSGE VMLPPLAYK  
 160 170 180 190 200  
 SACKIEVYI PFDQNTCLK FRKTYDTEI DMVLMPTA SMDQTFES  
 210 220 230 240 250  
 MDVALQGR TVNPDQSYV DVTYDFIR KELYTF  
 WYH **U** **U** **U** **U**  
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**CHRNA14**

10 20 30 40 50  
 MGGQGLPLL LLLLVACVIA QGNQERLLI ADLQNTQYN LRPASRVD  
 60 70 80 90 100  
 WWSLKLITL NLSLNREE ALTNWWM QWDFRQKQ FDFYQELVY  
 110 120 130 140 150  
 RVPSTMWRF DIVLENNDV VFEVALYCV LVSFDQIYV LPAFIFASQ  
 160 170 180 190 200  
 SISVYTFPD WQNCSLPQS QYTSNREIL QLSQEQDTI RWFIDFAP  
 210 220 230 240 250  
 TENGSAIQH RPARMLDFA APAQEAQKQ VYFVILLQK  
 WYH **U** **U** **U** **U**  
 \*\*\*

**CHRNA15**

10 20 30 40 50  
 MARAPLVL LGLLGRGVQ KNEELRYLV LFNNYDQGR PVREYPTV  
 60 70 80 90 100  
 ISLKYVTLN ISLNKEKEL TFEVWIGIIV QVRYLNRQ DQFQIETLV  
 110 120 130 140 150  
 FSELWLFIE VLENNIDQF QVAYDANIV YEGSYVLP PAIRSVCAV  
 160 170 180 190 200  
 EYTFPFRQV NCSLIFQDF YNAREVYTF AVNDQKTN KIDDTIAT  
 210 220 230 240 250  
 ENCAWIDFC FQVIRHBSG ATDQGETDV IYSLIRK  
 WYH **U** **U** **U** **U**  
 \*\*\*

**CHRNA16**

10 20 30 40 50  
 MESPVLGL LAALQGVGQ GMEKRLIR HLFQEQYKQ ELRVAFVH  
 60 70 80 90 100  
 SVDAALRL SNLISKQVE ETLITWVTE HWNTANLKR MAREFQIV  
 110 120 130 140 150  
 LGLPFWQV FEVLNNDQV QSPQISYCN VLVHYVYV MLFPAIRSS  
 160 170 180 190 200  
 CPISVYTF QWNCSLPQS SLKYAREIT LSLQDQNR RYTFVEMII  
 210 220 230 240 250  
 DEPTSEKQ MELVIRAVR WDFRPALES FERGQITFL IRK  
 WYH **U** **U** **U** **U**  
 \*\*\*

**CHRNA17**