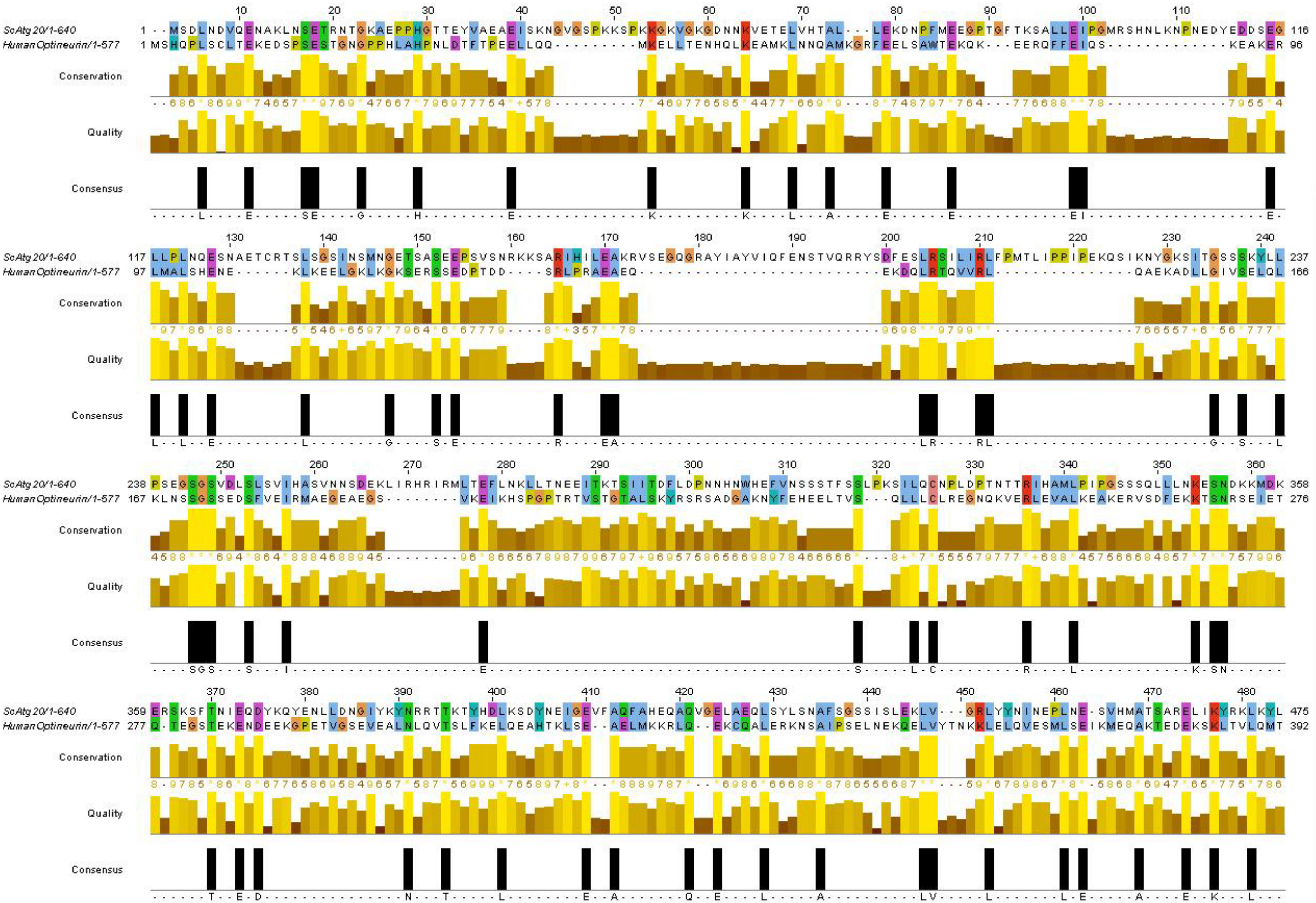
Supplemental Figures:

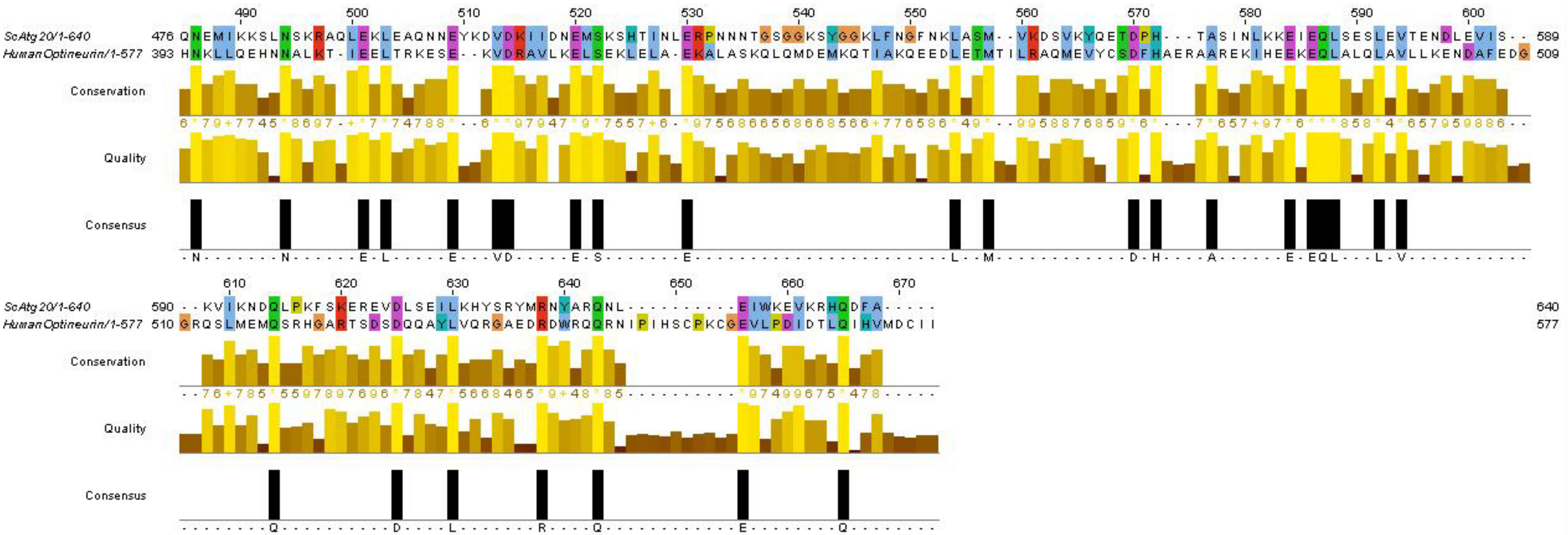
Supplemental figure alignments were done using EMBL-EBI MUltiple Sequence Comparison by Log-Expectation (MUSCLE, http://www.ebi.ac.uk/Tools/muscle/index.html)[1, 2] and Jalview Java Alignment Editor.[3, 4] The "Conservation" bars show amino acid property conservation, the "Quality" bars denote BLOSUM62 score based on observed substitutions, and the "Consensus" shows identical residues for pairwise alignments (Supplemental Figures 1, 3-7), or gives the commonest residues and their percentage for each column of the multialignment in Supplemental Figure 2.

1. Edgar RC. MUSCLE: a multiple sequence alignment method with reduced time and space complexity. BMC Bioinformatics 2004; 5:113.
2. Edgar RC. MUSCLE: multiple sequence alignment with high accuracy and high throughput. Nucleic Acids Res 2004; 32:1792-7.
3. Clamp M, Cuff J, Searle SM, Barton GJ. The Jalview Java alignment editor. Bioinformatics 2004; 20:426-7.
4. Waterhouse AM, Procter JB, Martin DM, Clamp M, Barton GJ. Jalview Version 2--a multiple sequence alignment editor and analysis workbench. Bioinformatics 2009; 25:1189-91.
5. Meijer WH, van der Klei IJ, Veenhuis M, Kiel JA. ATG genes involved in non-selective autophagy are conserved from yeast to man, but the selective Cvt and pexophagy pathways also require organism-specific genes. Autophagy 2007; 3:106-16.

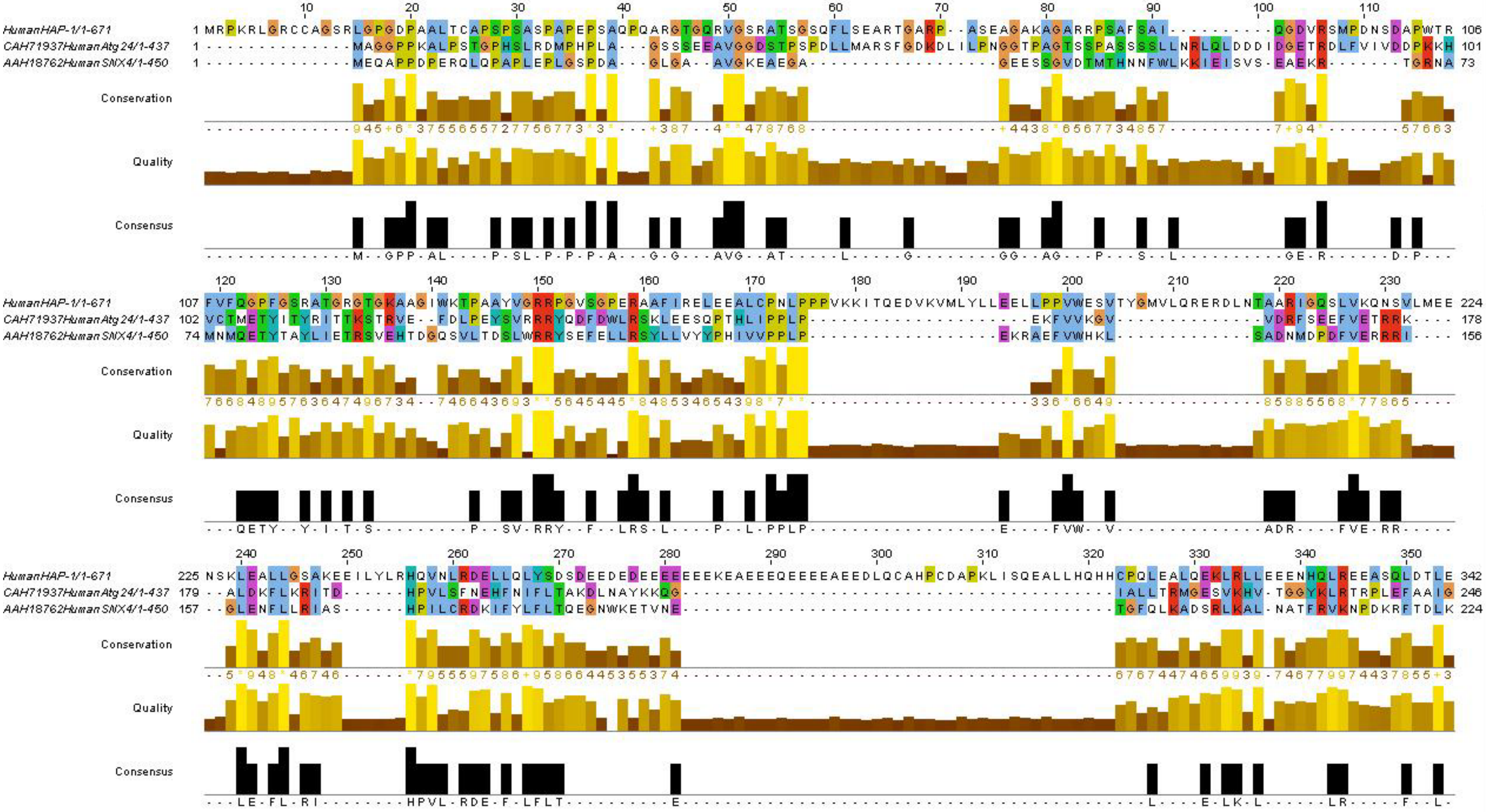
Supplemental Figure 1: *Saccharomyces cerevisiae* Atg20 has weak similarity to human Optineurin.



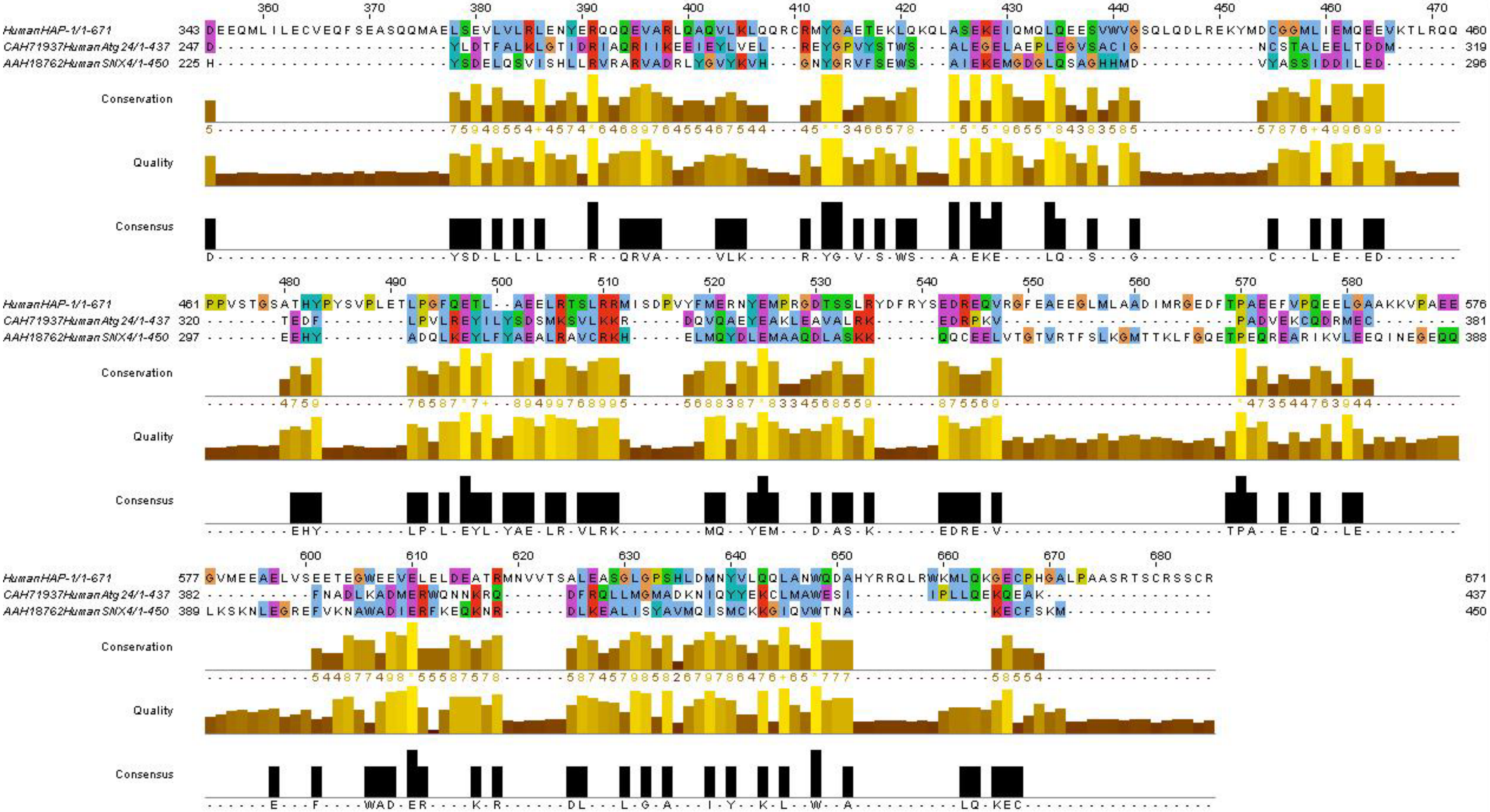
Supplemental Figure 1, continued



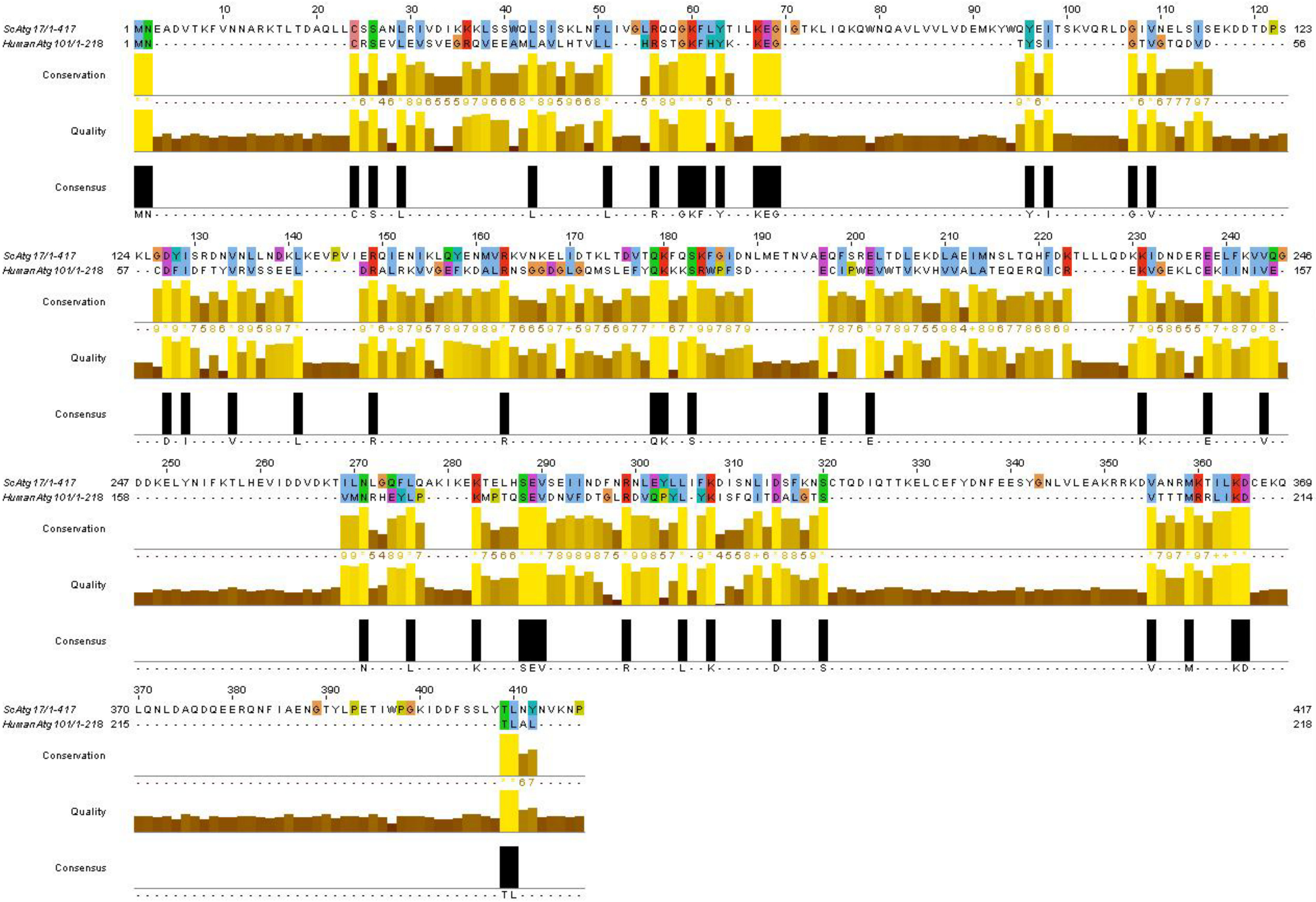
Supplemental Figure 2: Human Atg24/SNX4 homologs CAH71937 and AAH18762 ^{5} share some structural similarity with human HAP-1 protein.



Supplemental Figure 2, continued



Supplemental Figure 3: *Saccharomyces cerevisiae* Atg17 has weak similarity to human Atg101.



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ScAtg17/1-417          1 MNEADVTKFVNNARKTLTDAQLLCSSANLRIVDIKKKLSSWQLSISKLNFLIVGLRQQGKFLYTILKEGIGTKLIQKQWNQAVLVVLVDEMKYWQYEITSKVQRLDGIVNELSISEKDDTDPS 123
HumanAtg101/1-218      1 MN---------------------CRSEVLEVSVEGRQVEEAMLAVLHTVLL---HRSTGKFHYK--KEG-------------------------TYSI--------GTVGTQDVD-------- 56
Consensus                MN---------------------C-S--L-------------L-------L----R--GKF-Y---KEG--------------------------Y-I--------G-V--------------

ScAtg17/1-417        124 KLGDYISRDNVNLLNDKLKEVPVIERQIENIKLQYENMVRKVNKELIDTKLTDVTQKFQSKFGIDNLMETNVAEQFSRELTDLEKDLAEIMNSLTQHFDKTLLLQDKKIDNDEREELFKVVQG 246
HumanAtg101/1-218     57 --CDFIDFTYVRVSSEEL------DRALRKVVGEFKDALRNSGGDGLGQMSLEFYQKKKSRWPFSD-------ECIPWEVWTVKVHVVALATEQERQICR------EKVGEKLCEKIINIVE- 157
Consensus                ---D-I----V------L-------R-------------R---------------QK--S-------------E----E----------------------------K------E-----V--

ScAtg17/1-417        247 DDKELYNIFKTLHEVIDDVDKTILNLGQFLQAKIKEKTELHSEVSEIINDFNRNLEYLLIFKDISNLIDSFKNSCTQDIQTTKELCEFYDNFEESYGNLVLEAKRRKDVANRMKTILKDCEKQ 369
HumanAtg101/1-218    158 ----------------------VMNRHEYLP-----KMPTQSEVDNVFDTGLRDVQPYL-YKISFQITDALGTS----------------------------------VTTTMRRLIKD---- 214
Consensus                ------------------------N----L------K----SEV--------R-----L--K------D----S----------------------------------V---M----KD----

ScAtg17/1-417        370 LQNLDAQDQEERQNFIAENGTYLPETIWPGKIDDFSSLYTLNYNVKNP 417
HumanAtg101/1-218    215 ---------------------------------------TLAL----- 218
Consensus                ---------------------------------------TL------
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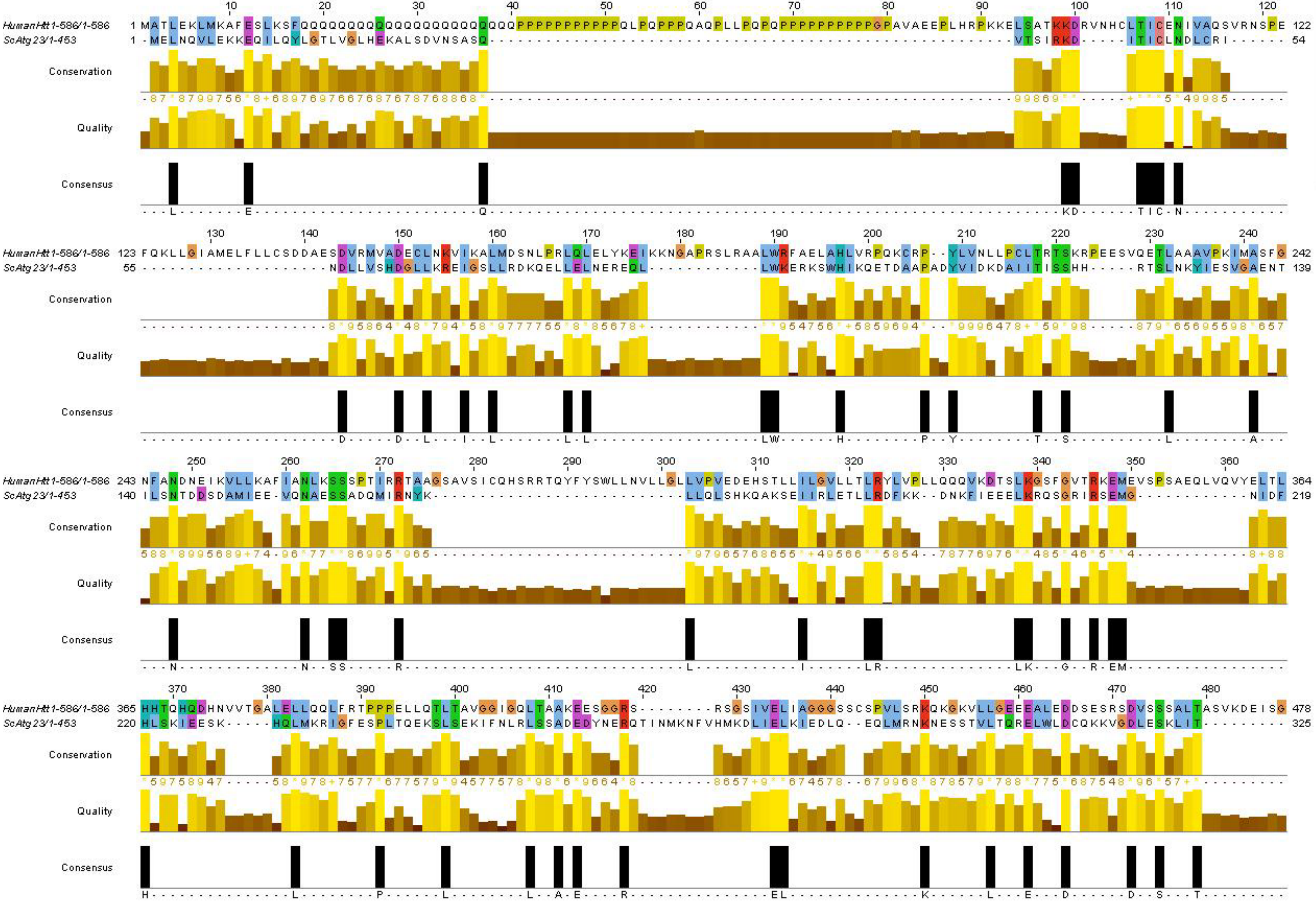
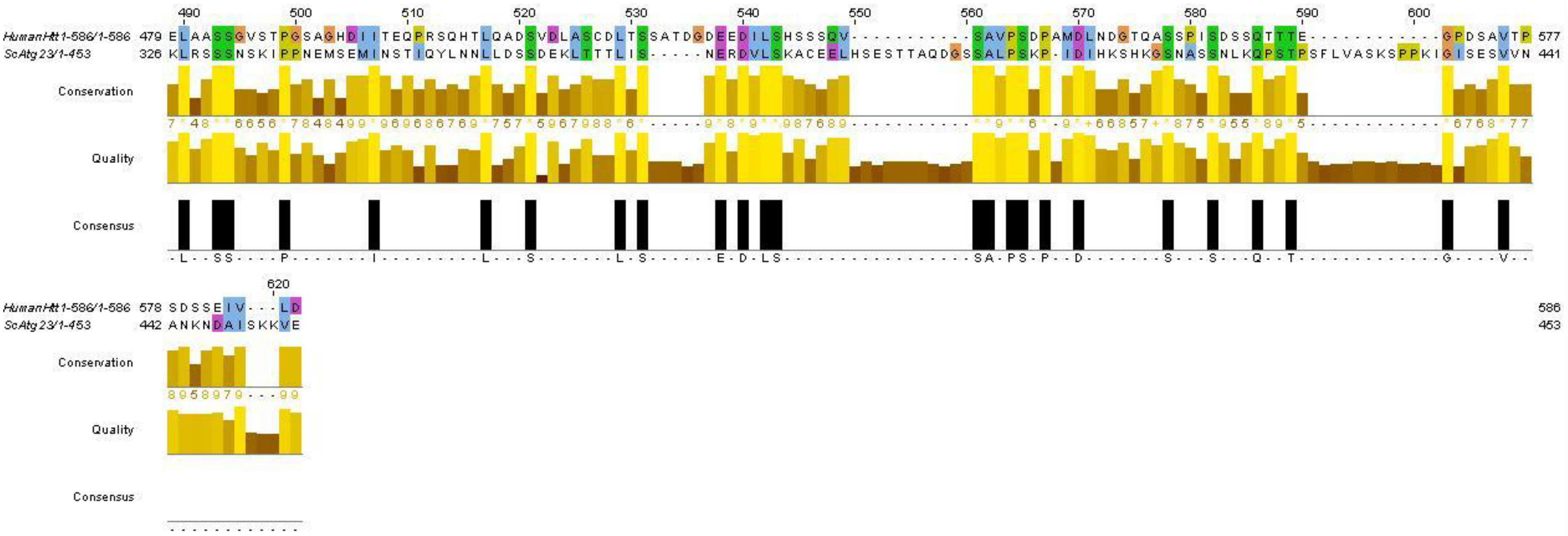
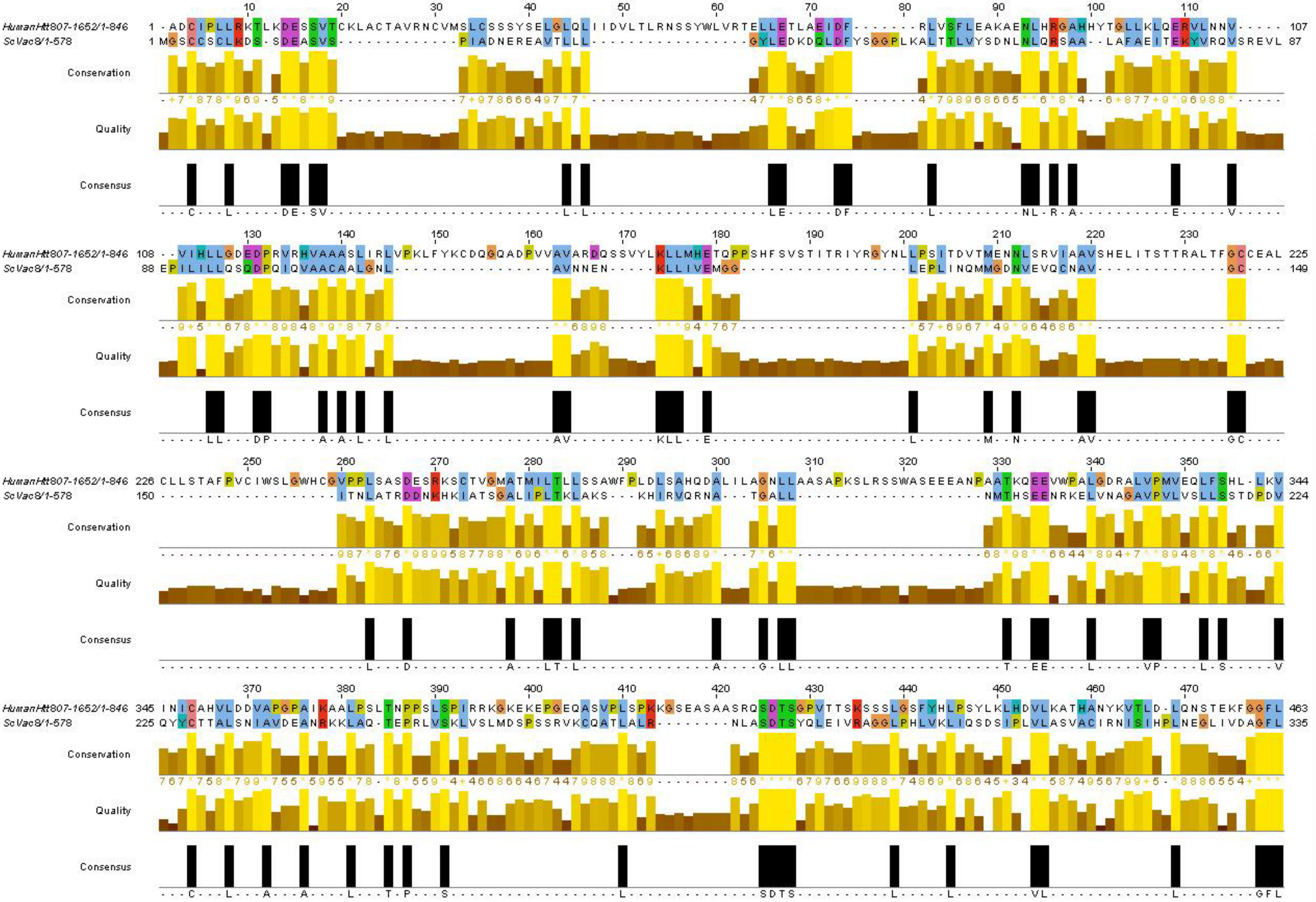
Supplemental Figure 4: The amino-terminal 586 amino acid caspase-6 cleavage fragment of human Htt is weakly similar to *Saccharomyces cerevisiae* Atg23.



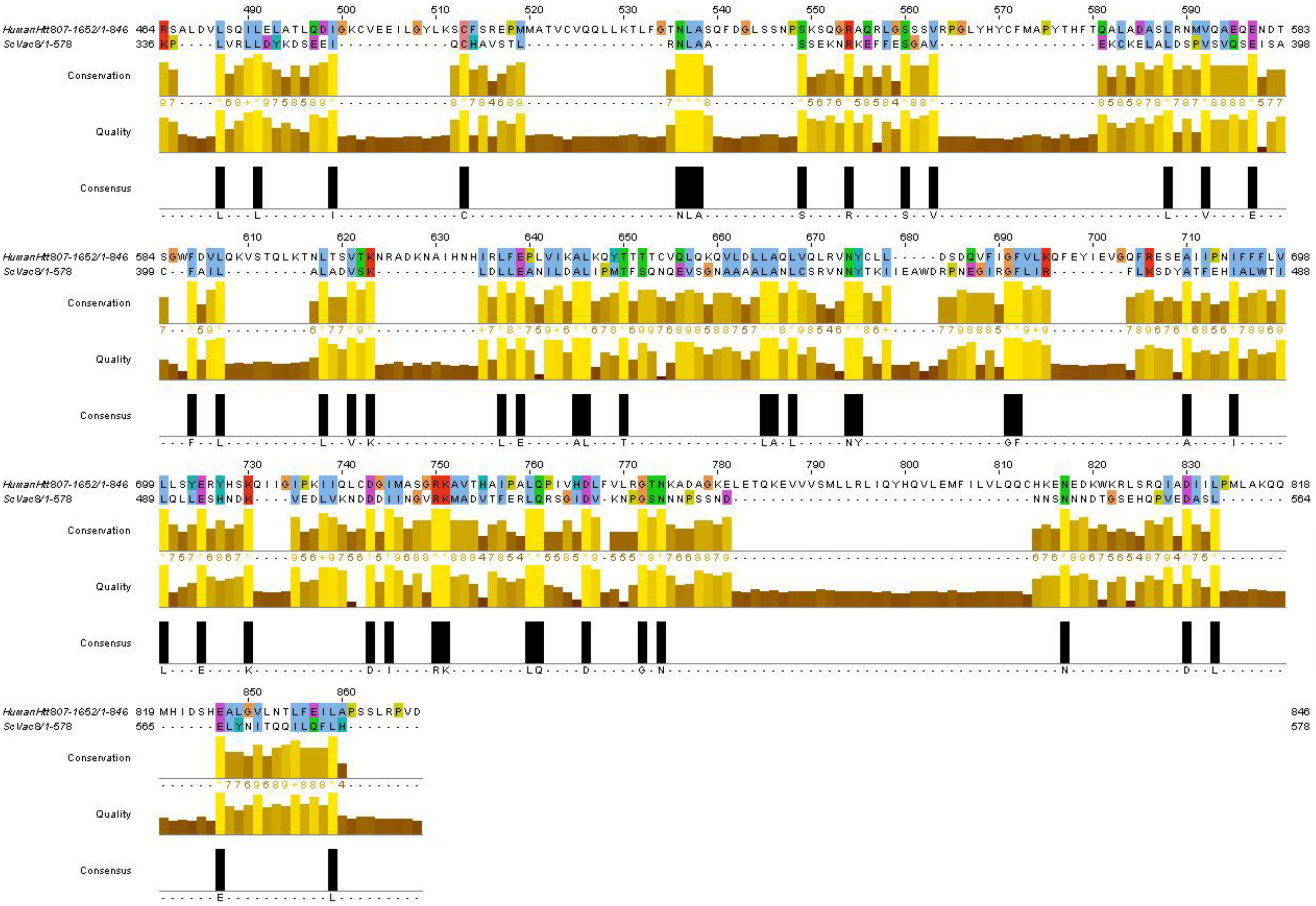
Supplemental Figure 4, continued



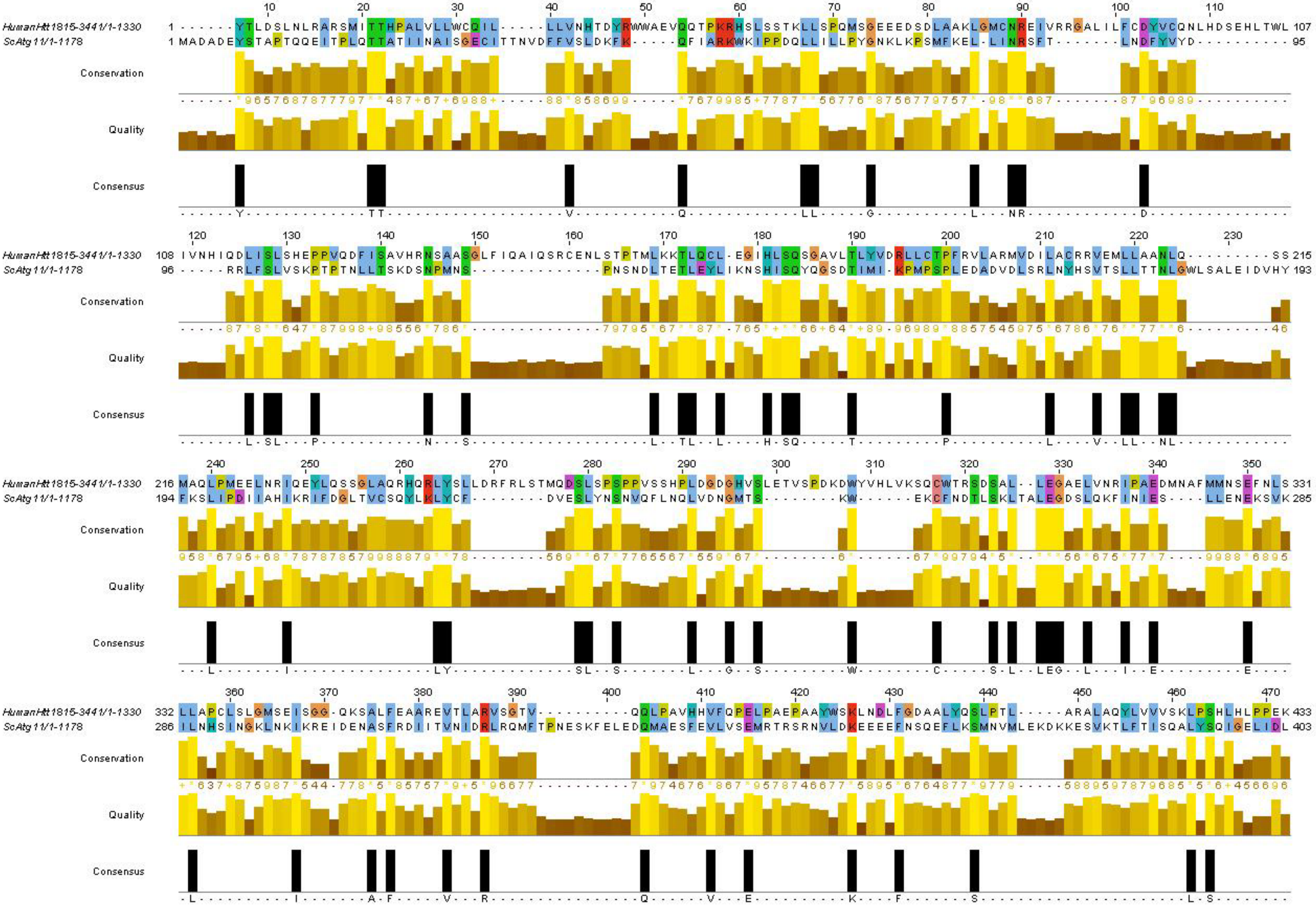
Supplemental Figure 5: The central domain of human Htt (amino acids 807-1652) has weak structural similarity to *Saccharomyces cerevisiae* Vac8.



Supplemental Figure 5, continued



Supplemental Figure 6: The carboxy-terminal domain of human Htt (amino acids 1815-3144) has weak similarity to *Saccharomyces cerevisiae* Atg11.



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HumanHtt1815-3441/1-1330   1 ------YTLDSLNLRARSMITTHPALVLLWCQIL-----LLVNHTDYRWWAEVQQTPKRHSLSSTKLLSPQMSGEEEDSDLAAKLGMCNREIVRRGALILFCDYVCQNLHDSEHLTWL 107
ScAtg11/1-1178             1 MADADEYSTAPTQQEITPLQTTATIINAISGECITTNVDFFVSLDKFK-----QFIARKWKIPPDQLLILLPYGNKLKPSMFKEL-LINRSFT--------LNDFYVYD----------- 95
Consensus                      ------Y-------------TT--------------------V-----------Q-------------LL-----G-----------L---NR--------------D-------------

HumanHtt1815-3441/1-1330 108 IVNHIQDLISLSHEPPVQDFISAVHRNSAASGLFIQAIQSRCENLSTPTMLKKTLQCL-EGIHLSQSGAVLTLYVDRLLCTPFRVLARMVDILACRRVEMLLAANLQ----------SS 215
ScAtg11/1-1178            96 -----RRLFSLVSKPTPTNLLTSKDSNPMNS---------------PNSNDLTETLEYLIKNSHISQYQGSDTIMI-KPMPSPLEDADVDLSRLNYHSVTSLLTTNLGWLSALEIDVHY 193
Consensus                      -------L-SL---P-------------N---S---------------------L---TL---L-----H-SQ------T---------P-----------L----V--LL--NL----------

HumanHtt1815-3441/1-1330 216 MAQLPMEELNRIQEYLQSSGLAQRHQRLYSLLDRFRLSTMQDSLSPSPPVSSHPLDGDGHVSLETVSPDKDWYVHLVKSQCWTRSDSAL--LEGAELVNRIPAEDMNAFMMNSEFNLS 331
ScAtg11/1-1178           194 FKSLIPDIIAHIKRIFDGLTVCSQYLKLYCF---------DVESLYNSNVQFLNQLVDNGMTS---------KW-------EKCFNDTLSKLTALEGDSLQKFINIES----LLENEKSVK 285
Consensus                      ---L-------I---------------LY-------------SL--S--------L---G--S-----------W----------C-----S-L--LEG--L---I--E----------E----

HumanHtt1815-3441/1-1330 332 LLAPCLSLGMSEISGG-QKSALFEAAREVTLARVSGTV-----------QQLPAVHHVFQPELPAEPAAYWSKLNDLFGDAALYQSLPTL-----ARALAQYLVVVSKLPSHLHLPPEK 433
ScAtg11/1-1178           286 ILNHSINGKLNKIKREIDENASFRDIITVNIDRLRQMFTPNESKFELEDQMAESFEVLVSEMRTRSRNVLDKEEEEFNSQEFLKSMNVMLEKDKKESVKTLFTISQALYSQIGELIDL 403
Consensus                      -L----------I--------A-F-----V---R-------------------Q-------V---E-----------K----F-------S-------------------L-S--------
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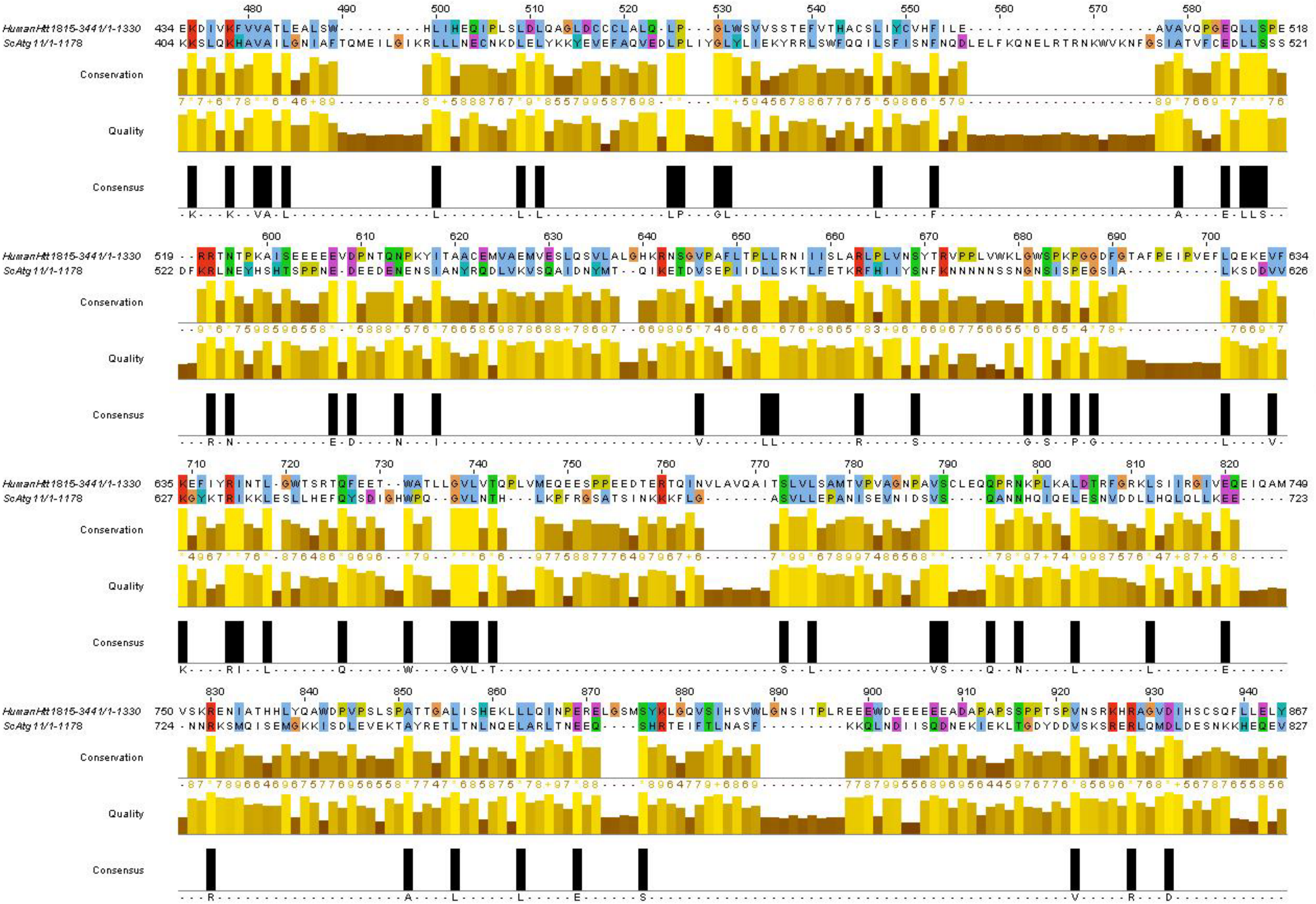
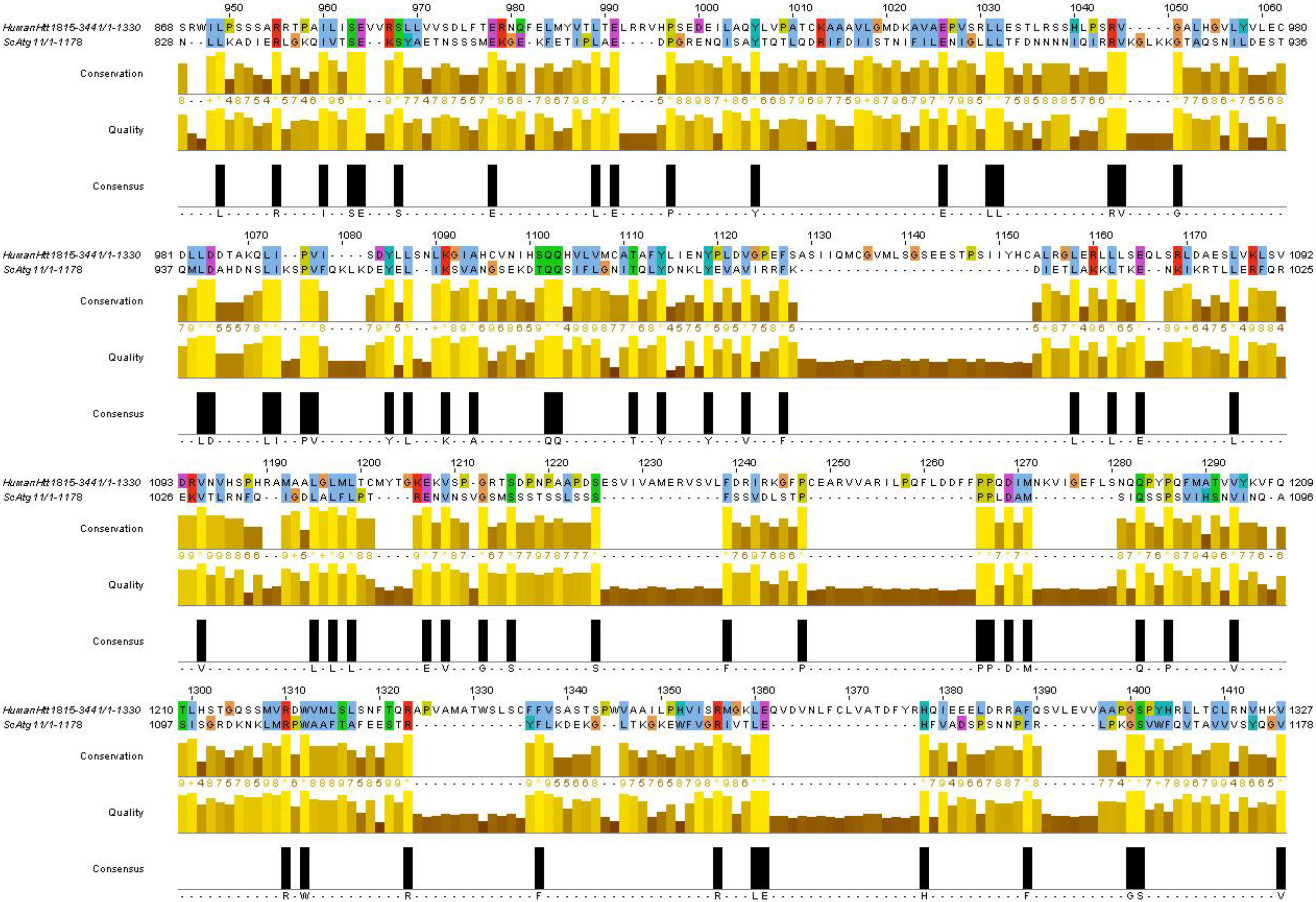
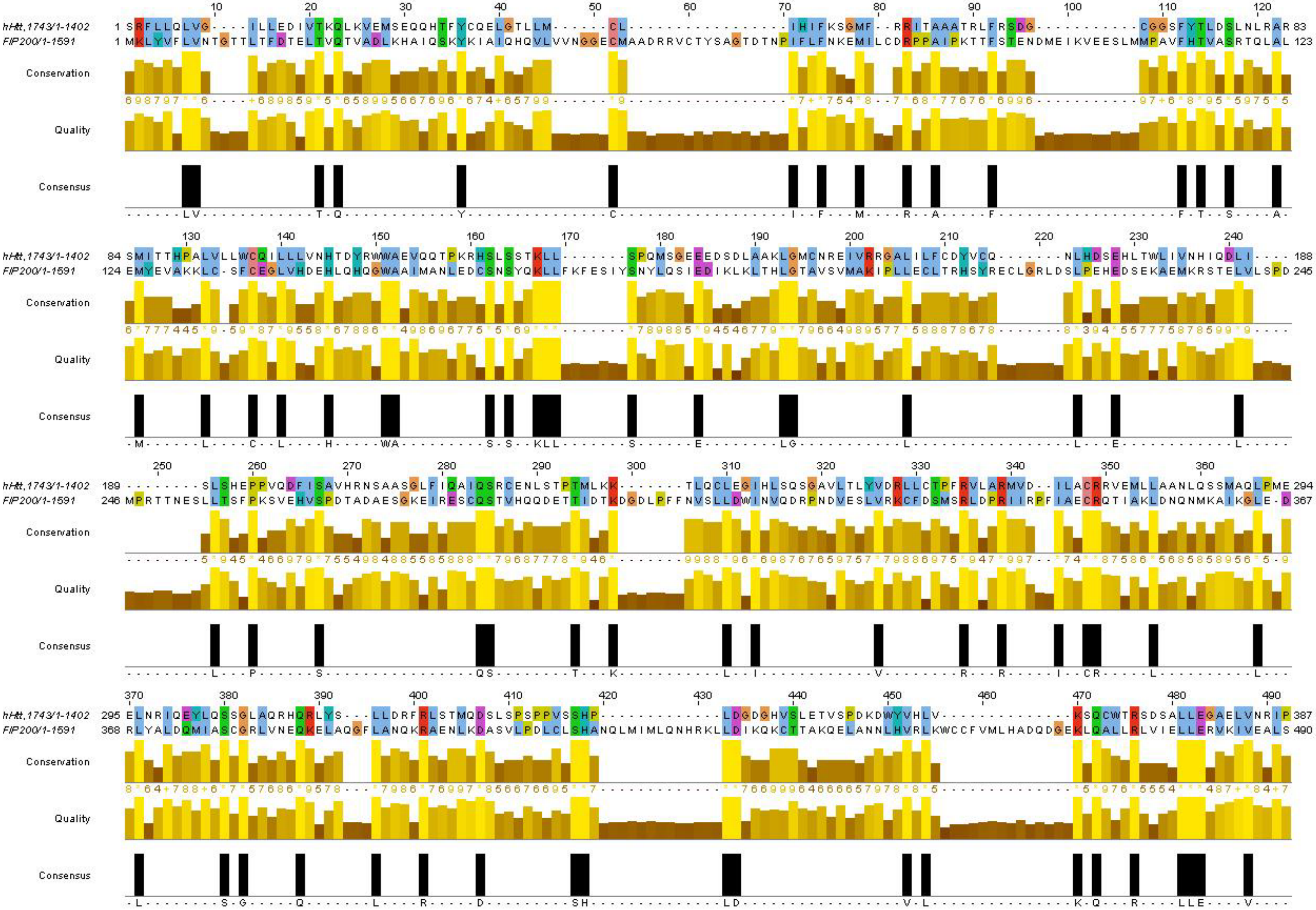
Supplemental Figure 6, continued



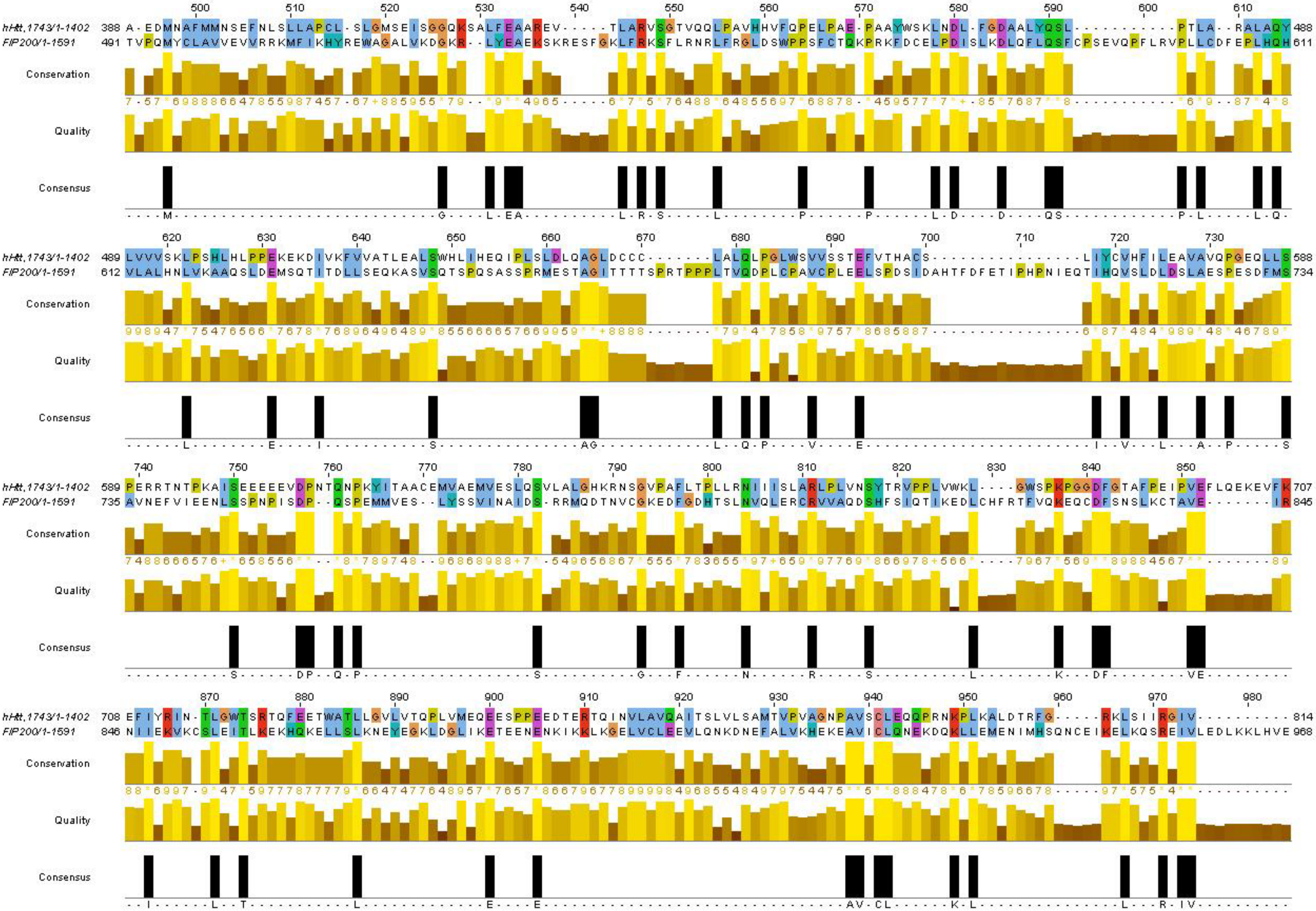
Supplemental Figure 6, continued



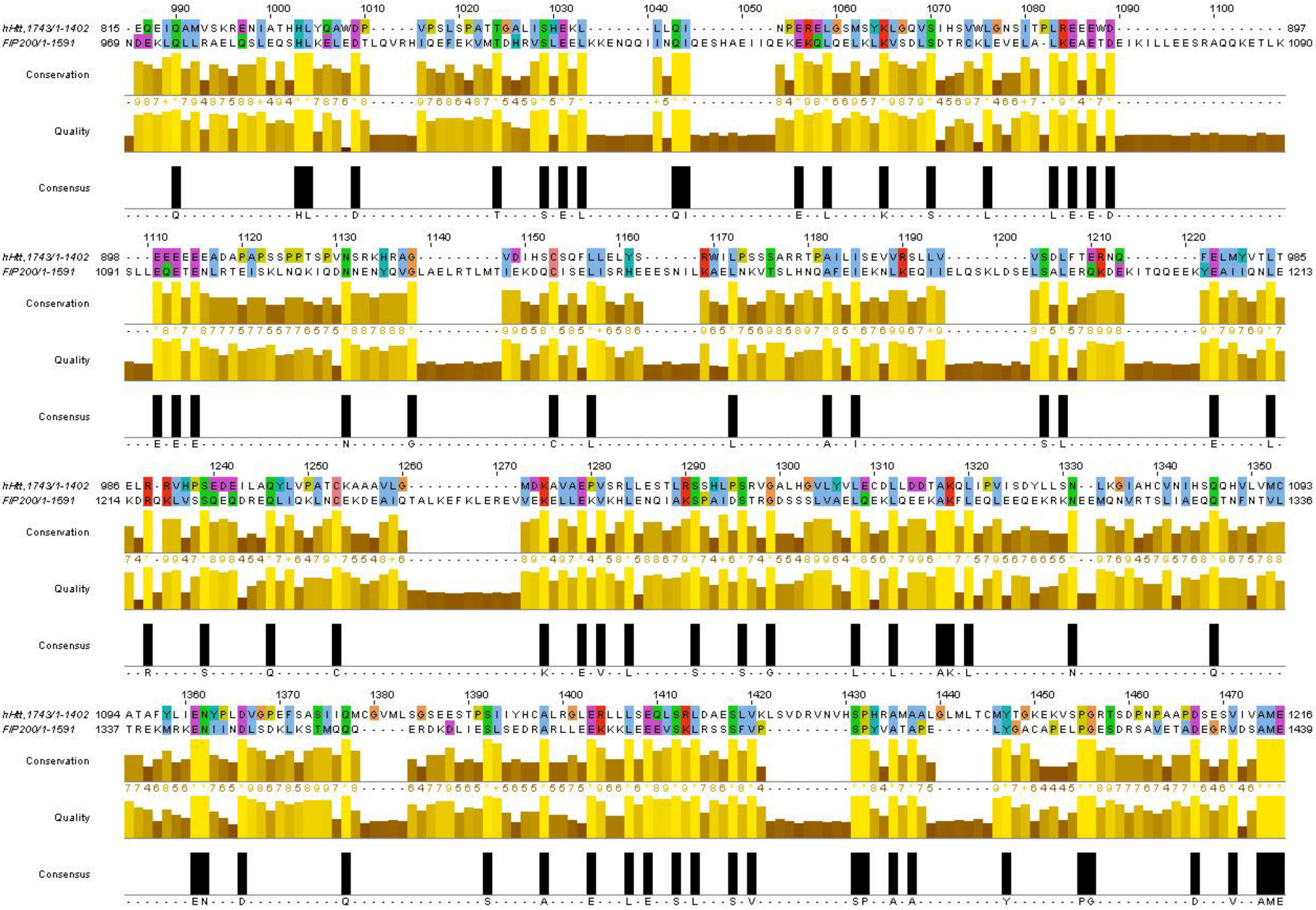
Supplemental Figure 7: Alignment of the carboxy-terminal domain of human Htt (amino acids 1743-3144) with human FIP200 total protein (amino acids 1-1591).



Supplemental Figure 7, continued



Supplemental Figure 7, continued



Supplemental Figure 7, continued