RESEARCH ARTICLE

Coevolution study of tau and α-synuclein suggests a connection between their normal interaction in neurons and the Parkinson's disease-associated mutation A53T

Author

James M. Gruschus

Laboratory of Structural Biophysics, National Heart, Lung & Blood Institute, National Institutes of Health, Bethesda, MD USA

Email: gruschuj@nih.gov

Abstract

Alpha-synuclein lies at the center of Parkinson's disease etiology, and polymorphisms in the gene for the microtubule-associated protein tau are risk factors for getting the disease. Tau and α-synuclein interact in vitro, and α-synuclein can also compete with tau binding to microtubules. To test whether these interactions might be part of their natural biological functions, a correlated mutation analysis was performed between tau and α-synuclein, looking for evidence of coevolution. For comparison, analyses were also performed between tau and β- and γ-synuclein. In addition, analyses were performed between tau and the synuclein proteins and the neuronal tubulin proteins. Potential correlated mutations were detected between tau and α-synuclein, one involving an α-synuclein residue known to interact with tau *in vitro*, Asn122, and others involving the Parkinson's disease-associated mutation A53T. No significant correlated mutations were seen between tau and β- and γ-synuclein. Tau showed potential correlated mutations with the neuron-specific βIII-tubulin protein, encoded by the *TUBB3* gene. No convincing correlated mutations were seen between the synuclein and tubulin proteins, with the possible exception of β-synuclein with βIVa-tubulin, encoded by the *TUBB4A* gene. While the correlated mutations between tau and α-synuclein suggest the two proteins have coevolved, additional study will be needed to confirm that their interaction is part of their normal biological function in cells.

Keywords: Correlated mutations analysis, mutual information, tauopathy, Alzheimer's disease, axon, neurodegenerative, intrinsically disordered protein, protein-protein interaction

Introduction

Pathology involving the protein α-synuclein is a defining feature of Parkinson's disease. A diagnosis of the disease can only be confirmed by observation of this pathology in neurons, in the form of Lewy bodies and neurites, proteinaceous deposits containing α-synuclein in its pathological, fibrillar form. In the brains of roughly 70% of Parkinson's disease patients, autopsy also reveals neurofibrillary tangles, distinct proteinaceous deposits containing the microtubule-associated protein tau in a fibrillar, hyperphosphorylated form. (1) Neurofibrillary tangles are a typical feature of Alzheimer's disease, as well as a group of neurodegenerative diseases known collectively as tauopathies.(2) Polymorphisms of the genes for α-synuclein and tau, *SNCA* and *MAPT*, respectively, are known risk factors for developing Parkinson's disease.(3)

In their monomeric, non-pathological forms, tau and α-synuclein can physically interact in vitro, and α-synuclein can also bind to microtubules, the natural interaction target of tau in neurons. (4) (5) Microtubules form part of the cytoskeleton of the cell and perform many vital roles, such as providing a conduit for the transport of proteins and other intracellular cargoes. Interaction with tau helps stabilize microtubule structure in axons and may play a role in modulating transport along microtubules. (6) (7) The microtubule structure is comprised of α-tubulin/β-tubulin heterodimer subunits, and in humans there are nine genes encoding α-tubulin proteins and nine genes encoding β-tubulin proteins. (8) Four of the β-tubulin genes are specifically expressed in brain tissue. (9) In contrast to tau, α-synuclein appears to have the opposite effect, destabilizing microtubule structure, and the mechanism of interaction, as well as whether it might play some regulatory role, is the subject of ongoing study. (5) Interaction between γ-synuclein and microtubules is also being studied. (10)

Given the high coincidence of tau and α-synuclein pathology and their interaction *in vitro*, this suggests their interaction might somehow promote the development of Parkinson's disease. This implication suggests a second possibility, namely, that the two proteins might interact in neurons as part of their normal biological function. They are both localized to neuronal axons, concentrated in presynaptic termini in the case of α-synuclein. To explore this question, this work presents a correlated mutation study of the two proteins to look for evidence that they have coevolved during the course of vertebrate evolution. The idea behind correlated mutation analysis is that for two interacting proteins, a mutation in one affecting the interaction might be compensated by a mutation in the other protein, such that functional interaction is maintained, leaving survival unaffected in the species. It is also possible that the second mutation modifies the interaction in way that might enhance survival. In either case, the pair of mutations could then be passed on to daughter species.

There are two other synuclein proteins in humans, β- and γ-synuclein, and for comparison, correlated mutation analyses of them with tau are also presented. In addition, because α-synuclein can possibly compete with tau for microtubule binding, analyses with the tubulin proteins that make up microtubules are presented, including four β-tubulins that are specific to brain tissue, βIIa-tubulin, βIIb-tubulin, βIII-tubulin, and βIVa-tubulin, and two non-tissue-specific tubulins, αIa-tubulin and βI-tubulin.

Methods

Multiple sequence alignments

The protein sequences of tau, α-, β-, and γ-synuclein, as well as αIa-tubulin (TUBA1A), βI-tubulin (TUBB), βIIa-tubulin (TUBB2A), βIIb-tubulin (TUBB2B), βIII-tubulin (TUBB3), and βIVa-tubulin (TUBB4A) were obtained from protein blast searches (blast.ncbi.nlm.nih.gov) using the human sequences as the initial query. For cases where the choice of ortholog was ambiguous, especially for the highly similar βIIa-tubulin and βIIb-tubulin proteins, human cDNA was also used as the query in a DNA blast search to identify the closest ortholog. The multiple sequence alignments from the blast searches were confirmed using Clustal Omega (www.ebi.ac.uk/Tools/msa/clustalo/). Sequences with missing regions or ambiguous residues were not used for analysis. In addition, protein sequences of interest could be missing from the annotated genomic sequence for particular species. In such cases, cDNA of a closely related species was used to search the full genomic sequence for the protein gene, but this typically resulted in only partial protein sequences being obtained. As a consequence, each pair of multiple sequence alignments (tau with α-synuclein, β-synuclein with βIVa-tubulin, etc.) used for the correlated mutation analyses typically included a different number of species. The residue numbering shown in figures corresponds to that of the human protein sequences. In places where the correlated mutation pairs include a position that corresponds to a gap in the human sequence in the multiple sequence alignment, the residue number is that of the residue immediately preceding the insertion, followed by a lowercase letter indicating the position in the insertion: 'a' for the first position in the insertion, 'b' for the second, and so on. In the notation for mutations, the letter for the human amino acid is given first, and when the human residue is not the ancestral residue, this is stated in the text.

Correlated mutation analysis

The correlated mutation analysis combines a mutual information correlation matrix with a global Z-score analysis of the matrix elements. This approach has been shown to be relatively robust when the number of species is limited, such as when analyzing vertebrate-specific proteins. (11) In the first step, the correlation matrix is calculated with the rows corresponding to the first protein sequence positions and the columns corresponding to the second protein sequence positions using the following equation

$$MI_{ij} = \sum_{m,n} f_{ij}(m,n) ln \left[\frac{f_{ij}(m,n)}{f_i(m) f_j(n)} \right]$$

where MI_{ij} is the mutual information value between position i in the first protein and position j in the second protein, $f_i(m)$ and $f_j(n)$ are the frequencies of amino acid types m and n at positions i and j, and $f_{ij}(m,n)$ is the frequency that m and n occur together in a species at positions i and j. The sum is taken over the 20 standard amino acids plus the gap, that is, each position can have one of 21 possibilities. Mutual information is similar to covariance, but it differs in that higher values are produced when a greater number of correlated mutations are present. The frequencies, $f_i(m)$, $f_j(n)$ and $f_{ij}(m,n)$ include a pseudocount correction of 1.5 to reduce the impact of sequencing errors on the *MI* values, the details of which are described elsewhere. (12)

In the second step, the Z-scores of each *MI* value were calculated. Z-scores correspond to how many standard deviations the *MI*

value for a particular pair of positions differ from the average *MI* for those positions with all other residue positions in the protein.

$$Z_{ij} = 0.5\left[(MI_{ij} - MI_{iav})/\sigma_i + (MI_{ij} - MI_{jav})/\sigma_j\right]$$

Where MI_{iav} is the average MI value between position *i* and all positions in the second protein sequence, MI_{jav} is the average MI value between position *j* and all positions in the first protein sequence, and σ_i and σ_j are the corresponding standard deviations. Higher Z-scores have been shown to be correlated with a higher probability that the two residue positions are in contact, and thus, have coevolved. (13)

Results

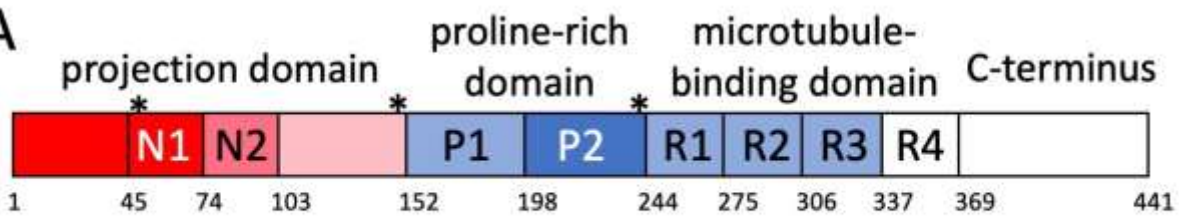
1. Tau and the tubulins

The top Z-scores for the correlated mutation analyses of tau with the six tubulin proteins are shown in figure 1. In humans, tau has six isoforms; the longest form, called 2N4R, has 441 residues. The shorter isoform sequences are subsets of the 2N4R sequence, having zero to two N-terminal inserts (N1, N2), and three or four highly conserved repeat domains (R1-R4) (figure 1a). The first 160 residues of 2N4R tau are highly variable, and there is almost no detectable homology in this region between fish and land vertebrates. Including more species in the analysis can improve the chance that the highest Z-score correlated mutation pairs correspond to genuinely interacting residues (12), so the analyses were repeated without the first 160 residues of tau, allowing the inclusion of fish species (except for βIIa-tubulin, which is amniote specific). The addition of fish species did not result in a net increase in the top Z-scores, however. For this reason, full-length 2N4R tau was used in all subsequent analyses.

Also shown in figure 1 are the top Z-scores for the analyses with the tubulin proteins using the hemoglobin beta chain as a negative control. In several cases, the Z-scores for hemoglobin exceed those for tau, which would seem to imply that tau and tubulins do not interact. This illustrates one of the weaknesses of correlated mutation analysis; to wit, the analysis cannot detect interacting residues where one or both is invariant. Roughly a third of tau residues are invariant, mostly in the C-terminal region, which is known to interact with microtubules (14), and over half of the tubulin residues are invariant. Thus, another possibility is that tau interactions with microtubules are dominated by interactions involving at least one invariant residue.

In two cases, the Z-scores with tau exceed those with hemoglobin, with β-tubulin and βIII-tubulin. The top five Z-score correlated pairs with βI-tubulin are shown in figure 2, βIII-tubulin in figure 3, and the other four tubulins in supplemental figure 1. Examination of figure 2 reveals another weakness of correlated mutation analysis; the residue pairs are only different in two frog species (*Xenopus tropicalis* and *Xenopus laevis*). This illustrates what is known as phylogenetic bias, or phylogenetic noise. The situation can arise where an ancestor of a branch in a family tree happens to have mutations in two non-interacting residues just by chance. All the daughter species will have the same pair of mutations (unless the residues mutate again).

A



B

Z-scores	αIa-tubulin	βI-tubulin	βIIa-tubulin	βIIb-tubulin	βIII-tubulin	βIVa-tubulin
tau	10.6	11.5	9.1	9.0	12.7	6.9
Δ_{N160}tau	10.8	11.3	9.7	9.1	11.7	5.9
hemo b	10.9	8.4	10.3	8.7	11.5	9.1

Figure 1. A) Diagram of the tau protein with four domains labeled and residue numbers shown at the start of each sub-region. At the N-terminus is the projection domain with N1 and N2 inserts, followed by the proline-rich domain with P1 and P2 sub-regions, followed by the microtubule-binding domain with four microtubule-binding repeats, followed by the C-terminus region. There are six isoforms of tau in humans, with both N1 and N2 inserts, with just N1, or with neither N1 nor N2 present, combined with microtubule-binding repeat R2 either present or absent. The projection domain is negatively charged, with the N-terminal and N1 insert having the most negative charge, indicated by the red color. The proline-rich domain is positively charged, with P2 having the most positive charge, indicated by the blue color. The microtubule-binding repeats R1, R2 and R3 have a modest net positive charge, while R4 and the C-terminus are net neutral. The asterisks mark the positions of mutations L48P, -149cG (see Methods for gap nomenclature), and S240A involved in correlated pairs with α-synuclein and βIII-tubulin. B) The top Z-scores from the correlated mutation analyses of tau with tubulin proteins found in neurons. The top line shows the Z-scores using full-length tau and the second line using tau excluding the first 160 residues (Δ_{N160}tau). For full-length tau, multiple sequence alignments of 123 vertebrate species on average were used in the analyses, while for Δ_{N160}tau the average number of species was 142. The bottom line shows the top Z-scores for hemoglobin beta chain with the tubulin proteins, as a negative control.

One of the advantages of the Z-score analysis is that the highest values correspond to the most unique patterns of mutations among species. If two chance mutations occur in an ancestor at a deep branch point in the tree, the mutation pattern will be shared by many ancestors, and thus will result in lower Z-scores. (13) However, if the mutation pair occurs at a shallow branch, or any branch with few daughter species, a higher Z-score can result. To get around this issue, an ideal correlated mutation pair should pass the "phylogenetic bias test," that is, the mutations should occur in two or more unrelated branches of the tree. Clearly, the top correlated mutation pairs of tau with βI-tubulin fail the test.

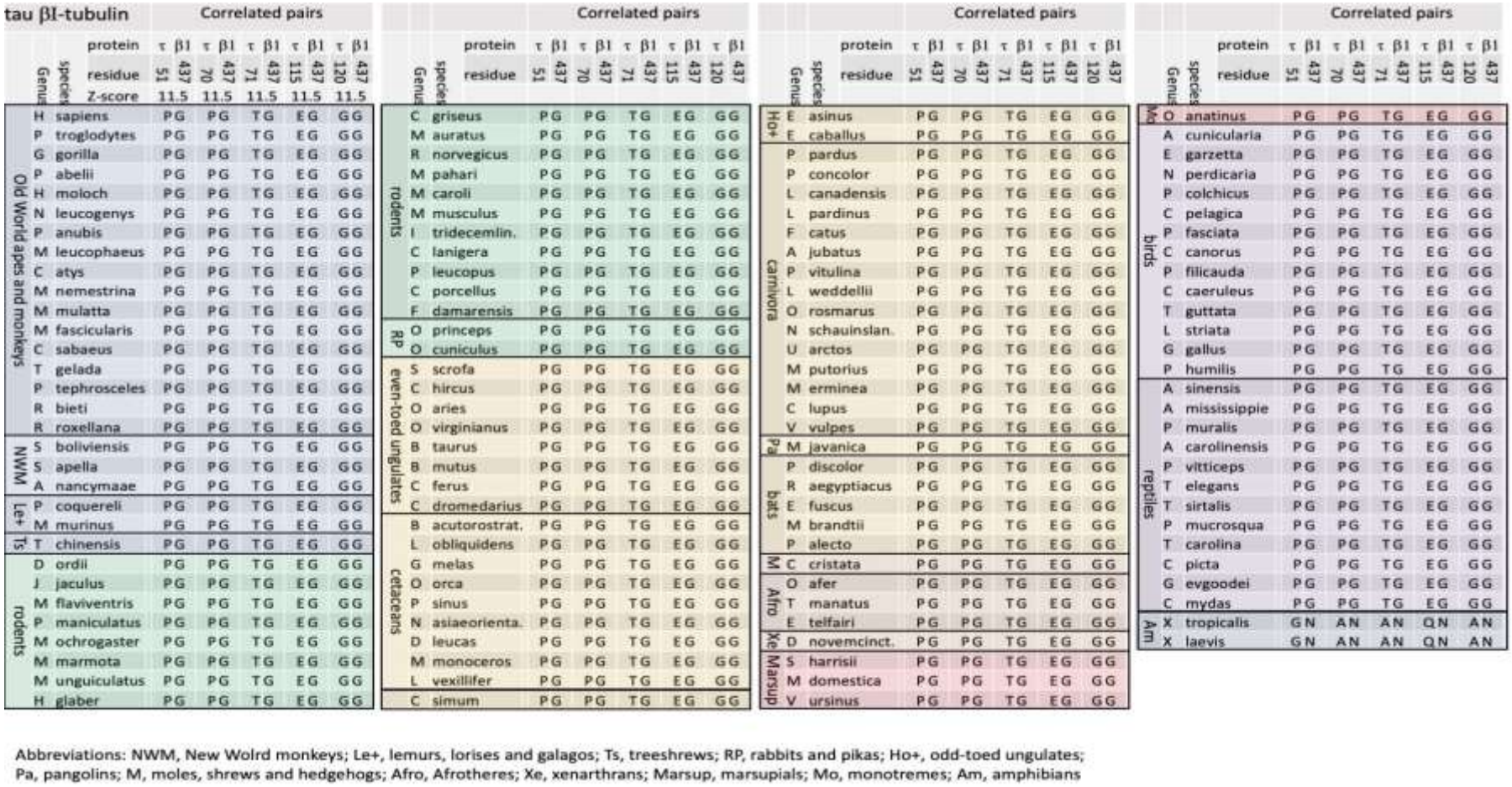


Figure 2. The top five correlated mutation pairs for tau with βI-tubulin. The correlated pairs are shown in five columns, with the corresponding residue numbers and Z-scores shown above. There is one row for each species in the multiple sequence alignment. The five columns are divided into four sections for more convenient display. The species are grouped roughly by class, order and/or suborder following standard conventions, and coloring indicates evolutionary distance from humans, blue for primates and more distantly related treeshrews, next green for rodents and glires (rabbits and pikas), yellow for Laurasiatheres (hoofed animals, cetaceans, carnivora, bats, etc.), orange for more distantly related placental mammals (moles, shrews, Afrotheres, xenarthrans, etc.), red for marsupials and more distantly related monotremes, purple for birds and reptiles, and dark blue for amphibians.

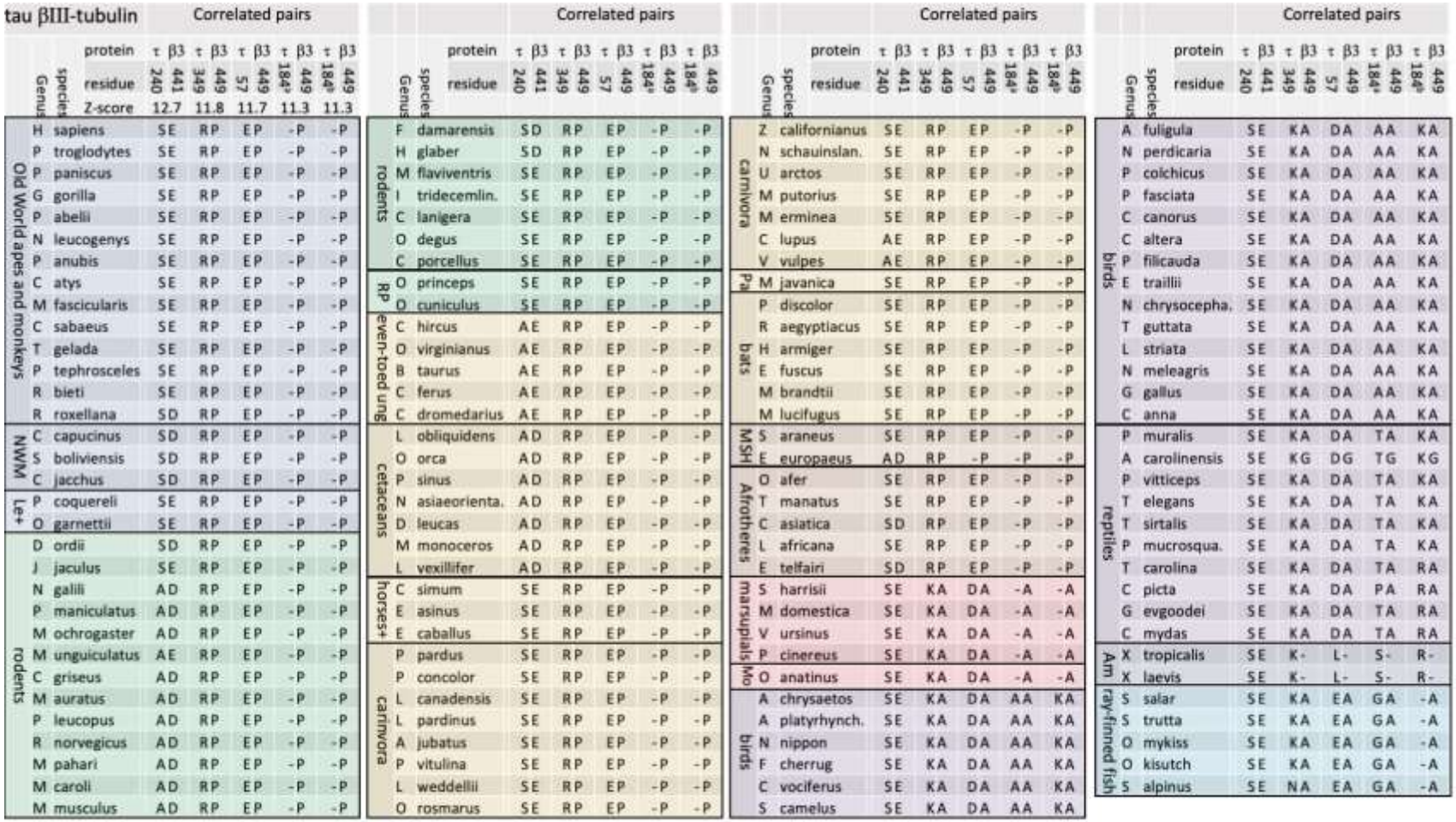


Figure 3. The top five correlated mutation pairs for tau with βIII-tubulin. See figure 2 for an explanation of the figure layout. Note that for tau with βIII-tubulin, there was a subset of ray-finned fish sequences with sufficient homology to land vertebrate sequences to be included in the correlated mutation analysis, and this group of species is shown in light blue.

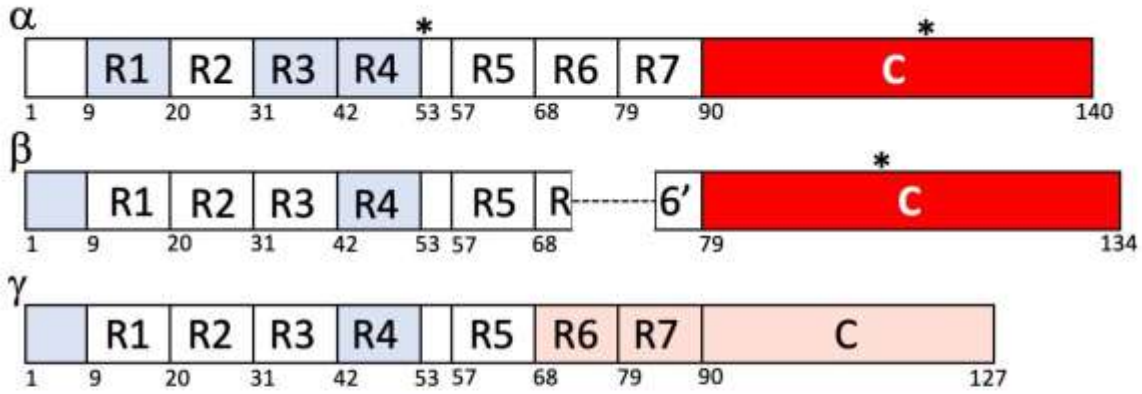
In contrast to βI-tubulin, the top correlated pair between tau and βIII-tubulin easily passes the phylogenetic bias test (figure 3). Whereas the majority of vertebrates have the pair SE (serine glutamate) in positions 240 and 441 of tau and βIII-tubulin, respectively, the pair AD (alanine aspartate) has arisen in three unrelated branches, in murids (mice and their kin), cetaceans, and in *Erinaceus europaeus* (European hedgehog). The intermediate pairs, SD and AE, are also seen for a few species; such transitional cases are not unexpected. This is because if either mutation were significantly deleterious to survival, it would be eliminated from the gene pool before the second mutation could occur. The remaining top correlated pairs shown in figure 3 do not pass the bias test, all reflecting the branching of mammals from the other vertebrates, with Z-scores similar to the control case with hemoglobin beta chain (figure 1). In summary, for tau and neuronal tubulin proteins found in neurons, the most convincing candidate for a genuine correlated mutation pair is the highest Z-score pair for tau and βIII-tubulin.

2. Tau and the synucleins

The top Z-scores of the correlated mutation analyses of tau with α-, β- and γ-synuclein and shown in figure 4, and with hemoglobin beta chain as a control. Synuclein proteins consist of a 78-89 amino acid N-terminal region consisting of six (for β-synuclein) or seven (for α- and γ-synuclein) imperfect 11-residue repeats, followed by a negatively charged C-terminal region 38-56 residues long (figure 4a). The highest Z-score correlated pair is seen with α-synuclein, and the top five correlated pairs of tau with α-synuclein are shown in figure 5. The top correlated pairs with β-synuclein and γ-synuclein are shown in supplemental figure 2.

The top tau/α-synuclein pair Z-score, 8.9, exceeds that of the hemoglobin control, 6.8, indicating a higher probability that the top pair could be a genuine correlated mutation. With β-synuclein and γ-synuclein, the top Z-scores are lower than hemoglobin. These results suggest that tau might have coevolved with α-synuclein, but not with β-synuclein and γ-synuclein. Caution is warranted, however, as the top correlated pair with α-synuclein fails the phylogenetic bias test, with the mutation pair occurring only in bovines.

A



B

Z-scores	α-synuclein	β-synuclein	γ-synuclein	hemo b
tau	8.9	5.6	5.5	6.8

Figure 4. A) Diagram of the synuclein proteins with the 11-residue imperfect repeats (R1-R7) and C-terminal tail (C) indicated with residue numbers shown at the beginning of each region. For β-synuclein the first five residues of the final repeat R6' are homologous to the corresponding residues in R6 of α- and γ-synuclein, and the final six residues are homologous to the corresponding residues in R7 of α- and γ-synuclein. The regions with moderate positive charge are shown in light blue, neutral charge in white, moderate negative charge in light red, and the most negative charge in red. The C-terminal tail of β-synculein is the most negatively charged (-16 over 56 residues), followed by α-synuclein (-12 over 51 residues), and γ-synuclein (-5 over 38 residues). The asterisks mark the positions of residues involved in correlated mutation pairs, A53T and N122S for α-synuclein with tau, and A102V in β-synuclein with βIVa-tubulin. B) The top Z-scores from the correlated mutation analyses of tau with the synuclein proteins, and with hemoglobin beta chain as a negative control.

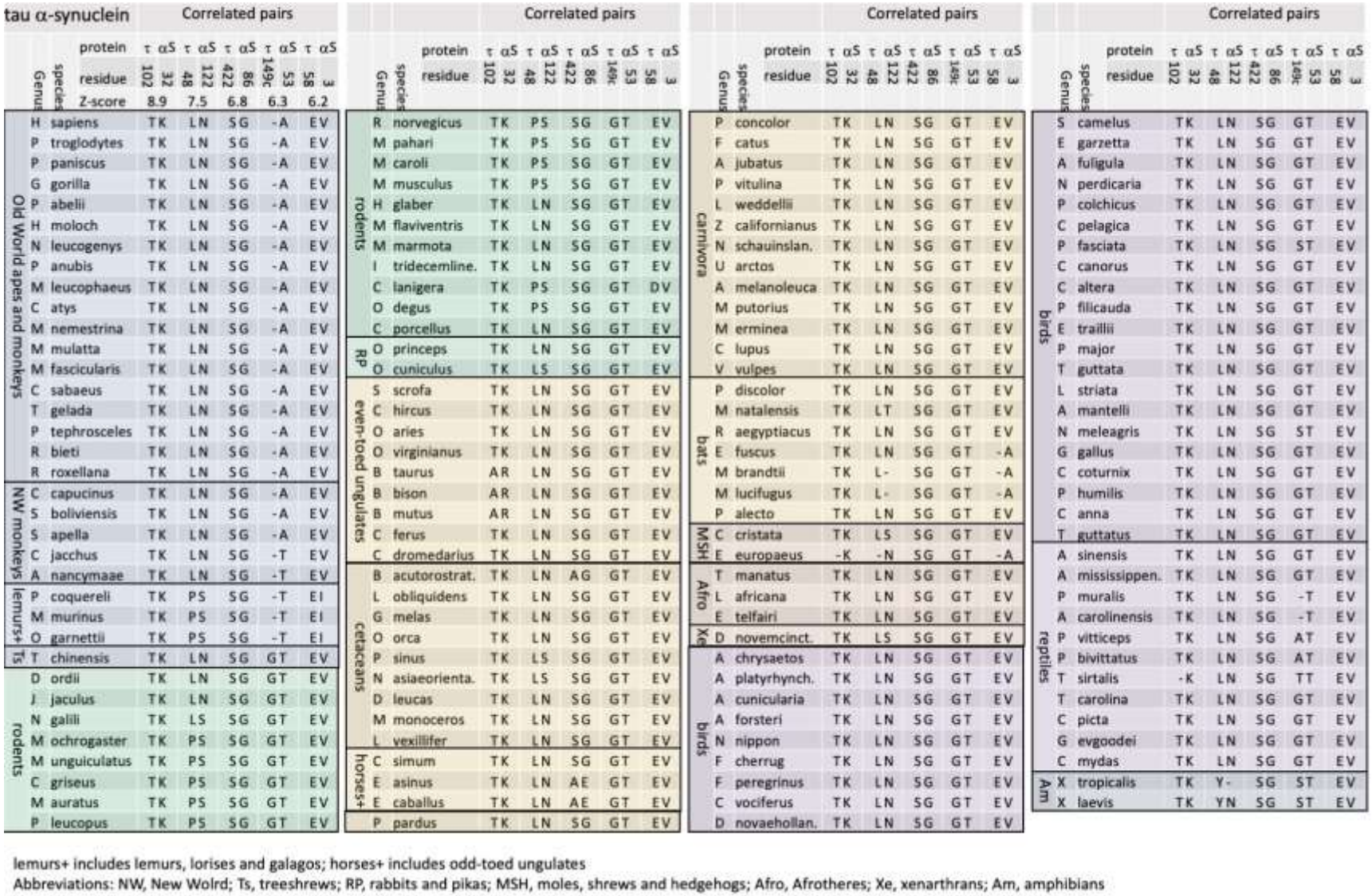


Figure 5. The top five correlated mutation pairs for tau with α-synuclein. See figure 2 for an explanation of the figure layout.

The second potential correlated mutation pair in figure 5, with a Z-score of 7.5 and involving residues 48 and 122 of tau and α-synuclein, respectively, *does* pass the phylogenetic bias test. Whereas the majority of vertebrates have the pair LN in these positions, the pair PS has arisen in strepsirrhines (lemurs, lorises and galagos), and in two branches of the rodent tree, in murids and in the common ancestor of *Chinchilla lanigera* and *Octodon degus* (common degu). The transitional pair LS is also seen in several species, but PN is not observed; if the correlated pair is genuine, perhaps the tau L48P mutation can only be accommodated after the N122S mutation in α-synuclein has already occurred.

The fourth highest Z-score correlated pair with α-synuclein is noteworthy because it involves a Mendelian mutation, A53T, known to cause an autosomal dominant familial form of Parkinson's disease. In this case, the human disease-causing residue T53 is the ancestral residue. The sixth and eighth highest correlated pairs also involve A53T (the sixth through tenth highest Z-score pairs for tau with α-synuclein are shown in supplemental figure 3). All these pairs seem to fail the phylogenetic bias test, since the A53T mutation pairs appear to have arisen just once in a putative common ancestor of apes, Old World monkeys, and the New World capuchin and squirrel monkeys (*Cebus capucinus*, *Saimiri boliviensis*, and *Sapajus apella*). This is curious, however, because in the standard primate phylogenetic tree (Tree of Life web project. http://tolweb.org/Primates/15963) New World monkeys are more closely related to each other than to Old World apes and monkeys. Assuming the standard tree is correct, there are two possibilities with different phylogenetic bias test outcomes. One possibility is that A53 arose just once in the ancestor of both Old and New World monkeys and reverted to the ancestral T53 in the marmoset *Callithrix jacchus* and night monkey *Aotus nancymaae*, thus failing the phylogenetic bias test. The other possibility is that the mutation to A53 arose twice, in the ancestor of Old World apes and monkeys and in the New World ancestor of capuchin and squirrel monkeys, in which case the test is satisfied.

3. The synucleins and the tubulins

The top Z-scores of the correlated mutation analyses of α-, β- and γ-synuclein with the six tubulin proteins are shown in figure 6, and with hemoglobin beta chain as a control. Unlike tau and the synucleins, which are intrinsically disordered in their monomeric, non-pathological forms, the tubulins fold into a highly conserved, well-defined GTPase protein structure, followed by a more variable, short C-terminal region rich in glutamate residues called the "E-hook" (figure 6a). The highest Z-score correlated mutation pairs are seen for β-synuclein with βIIa-tubulin and βIVa-tubulin; however, the top correlated pairs for βIIa-tubulin all fail the phylogenetic bias test. The top correlated pair for β-synuclein with βIVa-tubulin does pass the test, with mutations in two unrelated branches, for marsupials and for the afrothere *Chrysochloris asiatica*, and its top five correlated pairs are shown in figure 7. All the other top correlated pairs for α-, β- and γ-synuclein with the six tubulin proteins are shown in supplemental figure 4.

A

B

Z-scores	α1a-tubulin	βI-tubulin	βIIa-tubulin	βIIb-tubulin	βIII-tubulin	βIVa-tubulin
α-syn	10.8	8.7	8.5	9.6	11.7	7.6
β-syn	10.8	8.1	12.0	9.6	11.4	13.8
γ-syn	10.9	8.8	10.2	8.6	10.8	6.6
hemo b	10.9	8.4	10.3	8.7	11.5	9.1

Figure 6. A) Diagram of αIa- and the β-class tubulins with the three structural subdomains indicated with residue numbers shown at the beginning of each region. The N-terminal subdomain (N) contains the nucleotide binding site and has a moderate negative charge, shown by the light red color. The intermediate subdomain is net neutral for αIa-tubulin and has a moderate positive charge for the β-class tubulins. The C-terminal domain has the most negative charge, shown in red, and includes the flexible C-terminus "E-hook" region. The E-hook differs for the different β-class tubulins and is shown below, along with αIa-tubulin for comparison. The E-hook residues involved in correlated mutation pairs are highlighted in red, E441D for βIII-tubulin with tau, and -441aE for βIVa-tubulin with β-synuclein. B) The top Z-scores from the correlated mutation analyses with of the synuclein proteins with the tubulin proteins, with hemoglobin beta chain as a negative control.

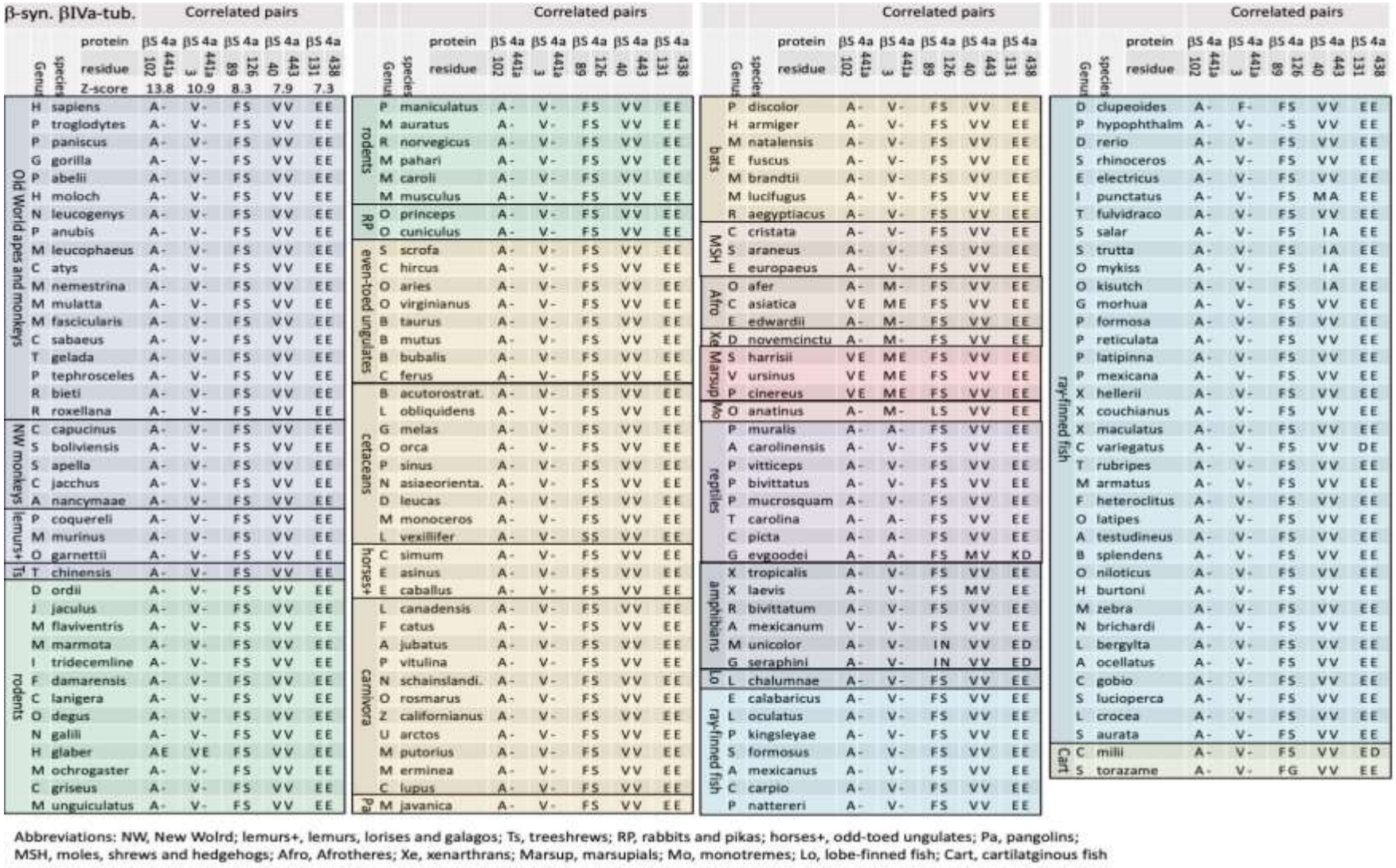


Figure 7. The top five correlated mutation pairs for β-synuclein with βIVa-tubulin. See figure 2 for an explanation of the figure layout. Note that for these two proteins, sequences from numerous fish species are known and included in the analysis, with one lobe-finned fish species in blue, ray-finned fish in light blue, and two cartilaginous fish in green. Also note that birds appear to lack βIVa-tubulin.

Unlike α- and γ-synuclein, there is no experimental evidence linking β-synuclein and microtubules that the author is aware of. Because of this, the potential correlated mutation pair with βIVa-tubulin should be viewed with extra caution. With all the combinations of three synuclein and six tubulin proteins, the odds increase that one combination might happen to have a non-interacting pair of mutations in two unrelated species, that is, the probability of the phylogenetic bias test producing a false positive is higher. Indeed, there are a few instances where top correlated pairs in the control analyses with hemoglobin also appear to pass the phylogenetic bias test (data not shown). Thus, compared to the other two cases of potential coevolution, tau with βIII-tubulin and tau with α-synuclein, the evidence for β-synuclein coevolving with βIVa-tubulin is less compelling.

Discussion

The results show potential correlated mutations pairs between tau and βIII-tubulin, between tau and α-synuclein, and perhaps between β-synuclein and βIVa-tubulin. Because microtubules are the natural binding target of tau, coevolution between tau and neuronally expressed tubulin proteins is a given. Indeed, it is surprising that the only convincing candidate for a bona fide correlated mutation pair is with βIII-tubulin. As explained in the results, correlated mutation analysis can only detect correlations between non-invariant residues, and it could be that most interactions between tau and tubulins involve at least one invariant residue.

The predicted correlated mutation pair for tau with βIII-tubulin does correspond to protein regions expected to interact, however. The tau mutation S240A occurs in the proline-rich region (figure 1a), which, along with the microtubule-binding repeat region, is necessary for strong binding. (14) The βIII-tubulin E441D mutation occurs in the E-hook, the flexible, glutamate-rich C-terminus which extends out from the microtubule where it can easily interact with binding proteins. Glutamate residues in the E-hook are often polyglutamylated, that is, chains of polyglutamate are attached to their side chains. While E441 is not a known polyglutamylation site, its near neighbor is, E438 (15), and another near neighbor, S444, is a phosphorylation site. Perhaps the mutation to aspartate can affect how the E-hook is modified.

The best candidate for a tau/α-synuclein correlated mutation pair, L48P for tau and N122S for α-synuclein, also corresponds to at least one region expected to interact based on previous experiments. Measured by NMR spectroscopy, N122 is one of the residues most perturbed by interaction with tau. (4) On the other hand, no significant perturbation of tau L48 was seen by interaction with α-synuclein; instead, the C-terminal half of the proline-rich region (P2 in figure 1a) was most strongly perturbed. Examining the net charges of the putative correlated pair regions also reveals a seeming discrepancy; both the tau N1 insert, wherein L48 lies (figure 1a), and the C-terminal domain of α-synuclein, containing N122 (figure 4a), are negatively charged. For interactions involving intrinsically disordered proteins, non-specific interactions between oppositely charged regions are more typical.(16) (17) Thus, it appears that L48 and N122 probably do not interact, at least not directly. Perhaps L48 and N122 compete for interaction with a third site, the positively charged proline-rich region of tau, as one possible example. In fact, there is evidence from fluorescence spectroscopy that the tau N1 and proline-rich regions interact.(18). The L48 site is flanked by two phosphorylation sites, S46 and T50,

and the L48P mutation might affect their phosphorylation, which, in turn, could impact electrostatic interactions with the N1 region. Nevertheless, until there is clear structural or functional evidence linking the tau L48 and α-synuclein N122 sites, this potential correlated mutation pair should be considered provisional.

The other tau/α-synuclein correlated mutation pair of interest involves the Parkinson's disease-associated mutation A53T in α-synuclein with -149cG for tau, where 149c- means the third position in the insert after human tau residue 149 in the multiple sequence alignment (see Methods), and G is the ancestral residue. The insert occurs right before the proline-rich domain. Because this mutation pair might have arisen only once, the chance of a false positive is high, that is, it might fail the phylogenetic bias test. On the other hand, it is also possible that it is a genuine correlated pair where the pair of mutations have so far happened only in Old World monkeys and apes, and New World squirrel and capuchin monkeys. In the NMR study cited above, the region around A53 seemed to show weak perturbations in the presence of tau, but below the threshold of significance. In another study of α-synuclein coevolution with the enzyme glucocerebrosidase, the top Z-score correlated pair involved α-synuclein A53T. (11) (12) Mutations in the gene for glucocerebrosidase, *GBA1*, are also risk factors for developing Parkinson's disease. It is intriguing that A53T comes up in both studies, hinting at a connection between disease-causing mutations and correlated mutation pairs, and in fact, such connections are observed for human genetic diseases in general. (19)

There are many proposed mechanisms for how the A53T mutation might cause Parkinson's disease in humans. Most are toxic gain-of-function hypotheses, where the mutation renders α-synuclein neurotoxic or promotes formation of its pathological oligomeric and amyloid forms. Recently, an alternate hypothesis has been proposed, that neurons overexpress the wild type allele to compensate loss-of-function caused by the mutated allele, causing overall α-synuclein levels to rise, thus increasing the likelihood of oligomer and amyloid formation. (20) Mutations linked to higher tau expression levels, in particular, those connected with the H1 haplotype, also appear to be associated with not just Parkinson's disease, but with Alzheimer's disease and many tauopathies as well. (21) (22) The tau -149cG mutation has not been detected in humans, though a nearby mutation A152T appears to be a risk factor for dementia with Lewy bodies, Alzheimer's disease and several tauopathies. (23) (24)

In conclusion, the correlated mutation analysis suggests that tau and α-synuclein might have coevolved, though more experimental evidence is needed to confirm this. The analysis yields more than just evidence of coevolution, however; the correlated mutation pairs can also provide clues regarding the normal biological function of the proteins, and the disease-causing mechanisms as well. Thus, genome sequencing of non-human species, vertebrates in particular, is a critical tool for understanding the origins of human disease.

Acknowledgements

This work was supported by the Intramural Research Program at the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI).

References

1. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. *Brain*. 2010;133(Pt6):1755-1762. doi:10.1093/brain/awq059
2. Zeng Y, Yang J, Zhang B, Gao M, Su Z, Huang Y. The structure and phase of tau: from monomer to amyloid filament. *Cell Mol Life Sci*. 2021;78(5):1873-1886. doi:10.1007/s00018-020-03681-x
3. Edwards TL, Scott WK, Almonte C, Burt A, Powell EH, Beecham GW, Wang L, Züchner S, Konidari I, Wang G, Singer C, Nahab F, Scott B, Stajich JM, Pericak-Vance M, Haines J, Vance JM, Martin ER. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. *Ann Hum Genet*. 2010;74(2):97-109. doi:10.1111/j.1469-1809.2009.00560.x
4. Siegert A, Rankovic M, Favretto F, et al. Interplay between tau and α-synuclein liquid-liquid phase separation [published online ahead of print, 2021 Jan 15]. Protein Sci. 2021;10.1002/pro.4025. doi:10.1002/pro.4025
5. Carnwath T, Mohammed R, Tsiang D. The direct and indirect effects of α-synuclein on microtubule stability in the pathogenesis of Parkinson's disease. *Neuropsychiatr Dis Treat*. 2018;14:1685-1695. doi:10.2147/NDT.S166322
6. Kadavath H, Hofele RV, Biernat J, et al. Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. *Proc Natl Acad Sci U S A*. 2015;112(24):7501-7506. doi:10.1073/pnas.1504081112
7. Melková K, Zapletal V, Narasimhan S, et al. Structure and functions of microtubule associated proteins tau and MAP2c: similarities and differences. *Biomolecules*. 2019;9(3):105. doi:10.3390/biom9030105
8. Roll-Mecak A. The tubulin code in microtubule dynamics and information encoding. *Dev Cell*. 2020;54(1):7-20. doi:10.1016/j.devcel.2020.06.008
9. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. *Science*. 2015;347(6220):1260419. doi:10.1126/science.1260419
10. Zhang H, Kouadio A, Cartledge D, Godwin AK. Role of gamma-synuclein in microtubule regulation. *Exp Cell Res*. 2011;317(10):1330-1339. doi:10.1016/j.yexcr.2010.10.013
11. Gruschus, JM. An evolutionary affair – the connection between Gaucher disease and Parkinson's disease. In *Synuclein and the Coelacanth – The Molecular and Evolutionary Origins of Parkinson's Disease*. Cambridge, MA, Academic Press, 2021:159-179. doi:10.1016/B978-0-323-85707-9.00015-0
12. Gruschus JM. Did α-synuclein and glucocerebrosidase coevolve? Implications for Parkinson's disease. *PLoS One*. 2015;10(7):e0133863. doi:10.1371/journal.pone.0133863
13. Dunn SD, Wahl LM, Gloor GB. Mutual information without the influence of phylogeny or entropy dramatically improves residue contact prediction. *Bioinformatics*. 2008;24(3):333-340. doi:10.1093/bioinformatics/btm604
14. Gustke N, Trinczek B, Biernat J, Mandelkow EM, Mandelkow E. Domains of tau protein and interactions with microtubules. *Biochemistry*. 1994;33(32):9511-9522. doi:10.1021/bi00198a017
15. Alexander JE, Hunt DF, Lee MK, et al. Characterization of posttranslational modifications in neuron-specific class III

beta-tubulin by mass spectrometry. *Proc Natl Acad Sci U S A*. 1991;88(11):4685-4689. doi:10.1073/pnas.88.11.4685

16. Ju JH, Maeng JS, Lee DY, Piszczek G, Gelmann EP, Gruschus JM. Interactions of the acidic domain and SRF interacting motifs with the NKX3.1 homeodomain. *Biochemistry*. 2009;48(44):10601-10607. doi:10.1021/bi9013374
17. Wu KP, Baum J. Detection of transient interchain interactions in the intrinsically disordered protein alpha-synuclein by NMR paramagnetic relaxation enhancement. *J Am Chem Soc*. 2010;132(16):5546-5547. doi:10.1021/ja9105495
18. McKibben KM, Rhoades E. Independent tubulin binding and polymerization by the proline-rich region of Tau is regulated by Tau's N-terminal domain. *J Biol Chem*. 2019;294(50):19381-19394. doi:10.1074/jbc.RA119.010172
19. Kowarsch A, Fuchs A, Frishman D, Pagel P. Correlated mutations: a hallmark of phenotypic amino acid substitutions. *PLoS Comput Biol*. 2010;6(9):e1000923. doi:10.1371/journal.pcbi.1000923
20. Gruschus, JM. Attack of the oligomers – alpha-synuclein amyloid oligomers and their pathogenic roles. In *Synuclein and the Coelacanth – The Molecular and Evolutionary Origins of Parkinson's Disease*. Cambridge, MA, Academic Press, 2021:129-158. doi:10.1016/B978-0-323-85707-9.00001-0
21. Kwok JB, Teber ET, Loy C, et al. Tau haplotypes regulate transcription and are associated with Parkinson's disease. *Ann Neurol*. 2004;55(3):329-334. doi:10.1002/ana.10826
22. Sánchez-Juan P, Moreno S, de Rojas I, et al. The *MAPT* H1 haplotype is a risk factor for Alzheimer's disease in APOE ε4 non-carriers. *Front Aging Neurosci*. 2019;11:327. doi:10.3389/fnagi.2019.00327
23. Labbé C, Ogaki K, Lorenzo-Betancor O, et al. Role for the microtubule-associated protein tau variant p.A152T in risk of α-synucleinopathies. *Neurology*. 2015;85(19):1680-1686. doi:10.1212/WNL.0000000000001946
24. Sydow A, Hochgräfe K, Könen S, et al. Age-dependent neuroinflammation and cognitive decline in a novel Ala152Thr-Tau transgenic mouse model of PSP and AD. *Acta Neuropathol Commun*. 2016;4:17. doi:10.1186/s40478-016-0281-z

SUPPLEMENTARY MATERIAL

Supplementary figures

1. The top five correlated mutation pairs for tau with A) αIa-tubulin, B) βIIa-tubulin, C) βIIb-tubulin and D) βIVa-tubulin.
2. The top five correlated mutation pairs for tau with A) β-synuclein and B) γ-synuclein.
3. The sixth through tenth highest correlated mutation pairs for tau with α-synuclein.
4. The top five correlated mutation pairs for α-synuclein with A) αIa-tubulin, B) βI-tubulin, C) βIIa-tubulin, D) βIIb-tubulin, E) βIII-tubulin, and F) βIVa-tubulin; for β-synuclein with G) αIa-tubulin, H) βI-tubulin, I) βIIa-tubulin, J) βIIb-tubulin, and K) βIII-tubulin; and for g-synuclein with L) αIa-tubulin, M) βI-tubulin, N) βIIa-tubulin, O) βIIb-tubulin, P) βIII-tubulin, and Q) βIVa-tubulin.

Supp. Fig. 1A

tau α1a-tubulin — Correlated pairs

Genus	species	protein	τ 1a	τ 1a	τ 1a	τ 1a	τ 1a
		residue	231	440	125	440	402	440	119	440	126	440
		Z-score	10.6	10.6	10.6	10.6	10.6
H	sapiens		TV	AV	DV	-V	RV
P	troglodytes		TV	AV	DV	-V	RV
G	gorilla		TV	AV	DV	-V	RV
P	abelii		TV	AV	DV	-V	RV
H	moloch		TV	AV	DV	-V	RV
N	leucogenys		TV	AV	DV	-V	RV
M	leucophaeu		TV	AV	DV	-V	RV
M	nemestrina		TV	AV	DV	-V	RV
M	mulatta		TV	AV	DV	-V	RV
M	fascicularis		TV	AV	DV	-V	RV
C	sabaeus		TV	AV	DV	-V	RV
P	tephrosele		TV	AV	DV	-V	RV
R	roxellana		TV	AV	DV	-V	RV
C	capucinus		TV	AV	DV	-V	RV
S	boliviensis		TV	AV	DV	-V	RV
S	apella		TV	AV	DV	-V	RV
C	jacchus		TV	AV	DV	-V	RV
A	nancymaae		TV	AV	DV	-V	RV
P	coquerel		TV	AV	DV	-V	RV
M	murinus		TV	AV	DV	-V	RV
O	garnettii		TV	AV	DV	-V	RV
D	ordii		TV	AV	DV	-V	RV
M	flaviventris		TV	AV	DV	-V	RV
M	marmota		TV	AV	DV	-V	RV
C	griseus		TV	AV	DV	-V	RV
R	norvegicus		TV	AV	DV	-V	RV
M	musculus		TV	AV	DV	-V	RV
I	tridecemlin		TV	AV	DV	-V	RV
P	leucopus		TV	AV	DV	-V	RV

Correlated pairs

Genus	species	protein	τ 1a	τ 1a	τ 1a	τ 1a	τ 1a
		residue	231	440	125	440	402	440	119	440	126	440
C	porcellus		TV	AV	DV	-V	RV
O	cuniculus		TV	EV	DV	-V	AV
S	scrofa		TV	AV	DV	-V	RV
C	hircus		TV	AV	DV	-V	RV
O	aries		TV	AV	DV	-V	RV
O	virginianus		TV	AV	DV	-V	RV
B	taurus		TV	AV	DV	-V	RV
B	bison		TV	AV	DV	-V	RV
B	mutus		TV	AV	DV	-V	RV
C	ferus		TV	AV	DV	-V	RV
L	obliquidens		TV	AV	DV	-V	RV
G	melas		TV	AV	DV	-V	RV
O	orca		TV	AV	DV	-V	RV
P	sinus		TV	AV	DV	-V	RV
D	leucas		TV	AV	EV	-V	RV
M	monoceros		TV	AV	EV	-V	RV
L	vexillifer		TV	AV	DV	-V	RV
C	simum		TV	AV	DV	-V	RV
E	asinus		TV	AV	DV	-V	RV
E	caballus		TV	AV	DV	-V	RV
P	pardus		TV	AV	DV	-V	RV
L	canadensis		TV	AV	DV	-V	RV
F	catus		TV	AV	DV	-V	RV
A	jubatus		TV	AV	DV	-V	RV
P	vitulina		TV	AV	DV	-V	RV
N	schauinslan		TV	AV	DV	-V	RV
U	arctos		TV	AV	DV	-V	RV
M	putorius		TV	AV	DV	-V	RV
M	erminea		TV	AV	DV	-V	RV

Correlated pairs

Genus	species	protein	τ 1a	τ 1a	τ 1a	τ 1a	τ 1a
		residue	231	440	125	440	402	440	119	440	126	440
C	lupus		TV	AV	DV	-V	RV
P	discolor		TV	AV	DV	-V	RV
R	aegyptiacus		TV	AV	DV	-V	RV
E	fuscus		TV	AV	DV	-V	RV
M	brandtii		TV	AV	DV	-V	RV
M	lucifugus		TV	AV	DV	-V	RV
O	afer		TV	AV	DV	-V	RV
C	asiatica		TV	AV	DV	-V	RV
L	africana		TV	AV	DV	-V	RV
D	novemcinct		TV	AV	DV	-V	RV
S	harrisii		TV	AV	DV	-V	RV
M	domestica		TV	AV	DV	-V	RV
P	cinereus		TV	EV	DV	-V	EV
O	anatinus		TV	AV	DV	-V	RV
F	peregrinus		TV	GV	DV	-V	RV
S	camelus		TV	AV	DV	-V	RV
A	fulgula		TV	AV	DV	-V	RV
C	altera		TV	GV	DV	-V	RV
P	filicauda		TV	GV	DV	-V	RV
T	guttata		TV	GV	DV	-V	RV
G	gallus		TV	AV	DV	-V	RV
C	japonica		TV	AV	DV	-V	RV
P	humilis		TV	GV	DV	-V	RV
C	anna		TV	GV	DV	-V	RV
T	guttatus		TV	AV	VV	-V	RV
P	muralis		TV	AV	DV	-V	RV
A	carolinensis		TV	AV	DV	-V	RV
P	vitticeps		TV	AV	DV	-V	RV
T	elegans		TV	AV	EV	-V	HV

Correlated pairs

Genus	species	protein	τ 1a	τ 1a	τ 1a	τ 1a	τ 1a
		residue	231	440	125	440	402	440	119	440	126	440
P	mucrosquam		TV	AV	DV	-V	HV
G	evgoodei		TV	AV	DV	-V	HV
X	tropicalis		TV	EV	EV	-V	KV
X	laevis		TV	EV	EV	-V	KV
S	salar		TI	AI	DI	TI	RI
S	trutta		TI	AI	DI	TI	RI
O	mykiss		TI	AI	DI	TI	RI
O	kisutch		TI	AI	DI	TI	RI
P	formosa		SI	-I	SI	TI	-I
P	latipinna		SI	-I	SI	TI	-I
P	mexicana		SI	-I	SI	TI	-I
X	hellerii		SI	-I	SI	TI	-I
X	couchianus		SI	-I	SI	TI	-I
X	maculatus		SI	-I	SI	TI	-I
M	armatus		SI	-I	SI	TI	-I
F	heterocitus		SI	-I	SI	TI	-I
O	latipes		SI	-I	SI	TI	-I
A	testudineus		SI	-I	SI	TI	-I
B	splendens		SI	-I	SI	TI	-I
O	niloticus		SI	-I	SI	TI	-I
H	burtoni		SI	-I	SI	TI	-I
M	zebra		SI	-I	SI	TI	-I
N	brichardi		SI	-I	SI	TI	-I
L	bergylta		SI	-I	SI	TI	-I
C	gobio		SV	-V	SV	TV	-V
S	lucioperca		SI	-I	SI	-I	-I
L	crocea		SI	-I	SI	TI	-I
S	aurata		SV	-V	SV	TV	-V

Supp. Fig. 1B

tau βIIa-tubulin — Correlated pairs

Genus	species	protein	τ 2A	τ 2A	τ 2A	τ 2A	τ 2A
		residue	2	443	109	48	306	48	167	48	184	440
		Z-score	10.2	9.0	9.0	9.0	8.4
H	sapiens		AD	GN	VN	NN	-E
P	troglodytes		AD	GN	VN	NN	-E
P	paniscus		AD	GN	VN	NN	-E
G	gorilla		AD	GN	VN	NN	-E
P	abelii		AD	GN	VN	NN	-E
N	leucogenys		AD	GN	VN	NN	-E
P	anubis		AD	GN	VN	NN	-E
C	atys		AD	GN	VN	NN	-E
M	nemestrina		AD	GN	VN	NN	-E
M	mulatta		AD	GN	VN	NN	-E
M	fascicularis		AD	GN	VN	NN	-E
C	sabaeus		AD	GN	VN	NN	-E
T	gelada		AD	GN	VN	NN	-E
R	roxellana		AD	GN	VN	NN	-E
S	boliviensis		AD	GN	VN	NN	-E
C	jacchus		AD	GN	VN	NN	-E
M	murinus		AD	GN	VN	NN	-E
N	galili		AD	GN	VN	NN	-E
D	ordii		AD	GN	VN	NN	-E
P	maniculatus		AD	GN	VN	NN	-E
M	ochrogaster		AD	GN	VN	NN	-E
M	marmota		AD	GN	VN	NN	-E
C	griseus		AD	GN	VN	NN	-E
M	auratus		AD	GN	VN	NN	-E
R	norvegicus		AD	GN	VN	NN	-E
M	musculus		AD	GN	VN	NN	-E
I	tridecemlin		AD	GN	VN	NN	-E
C	lanigera		AD	GN	VN	NN	-E

Correlated pairs

Genus	species	protein	τ 2A	τ 2A	τ 2A	τ 2A	τ 2A
		residue	2	443	109	48	306	48	167	48	184	440
P	leucopus		-D	GN	VN	NN	-E
C	porcellus		AD	GN	VN	NN	-E
F	damarensis		AD	GN	VN	NN	-E
O	degus		AD	GN	VN	SN	-E
O	princeps		AD	GN	VN	NN	-E
O	cuniculus		AD	GN	VN	NN	-E
S	scrofa		AD	GN	VN	NN	-E
C	hircus		AD	GN	VN	NN	-E
O	aries		AD	GN	VN	NN	-E
B	taurus		AD	GN	VN	NN	-E
B	bison		AD	GN	VN	NN	-E
C	ferus		AD	GN	VN	NN	-E
C	dromedariu		AD	GN	VN	NN	-E
B	acutorostrat		AD	GN	VN	NN	-E
L	obliquidens		AD	GN	VN	NN	-E
O	orca		AD	GN	VN	NN	-E
P	sinus		AD	GN	VN	NN	-E
D	leucas		AD	GN	VN	NN	-E
M	monoceros		AD	GN	VN	NN	-E
L	vexillifer		AD	GN	VN	NN	-E
C	simum		AD	GN	VN	NN	-E
E	caballus		AD	GN	VN	NN	-E
P	pardus		AD	GN	VN	NN	-E
L	canadensis		AD	GN	VN	NN	-E
F	catus		AD	GN	VN	NN	-E
A	jubatus		AD	GN	VN	NN	-E
P	vitulina		AD	GN	VN	NN	-E
L	weddellii		AD	GN	VN	NN	-E

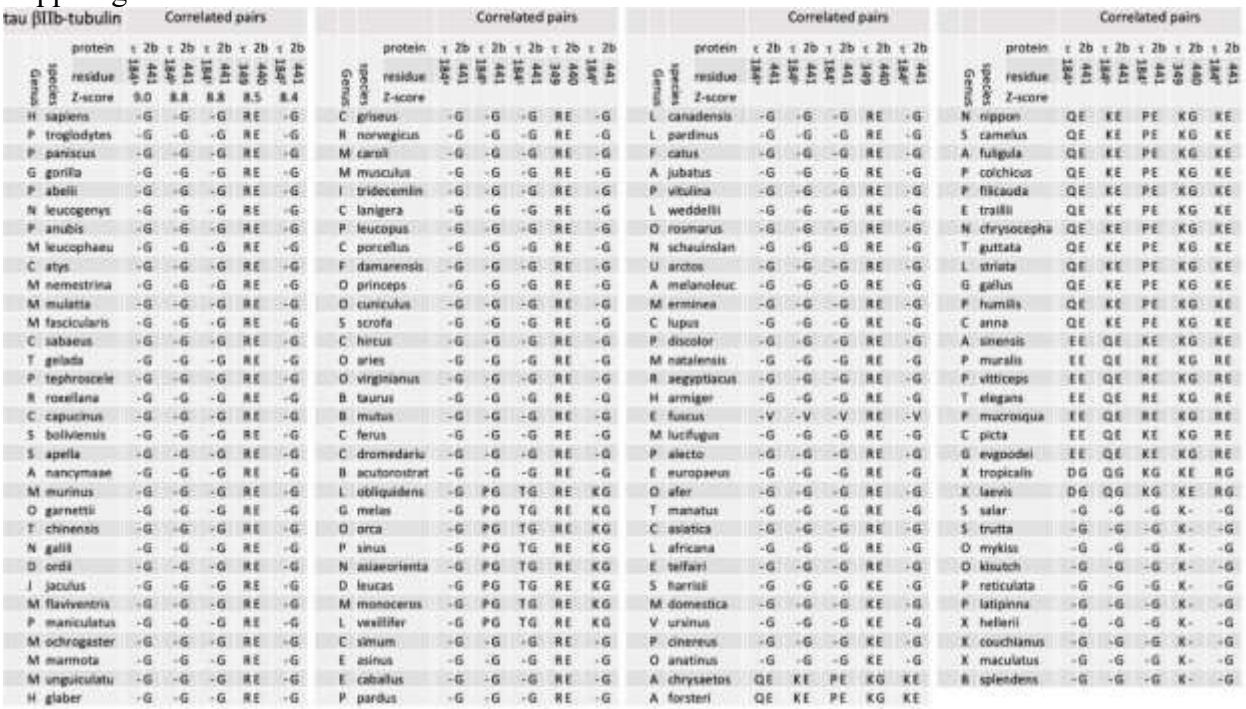
Correlated pairs

Genus	species	protein	τ 2A	τ 2A	τ 2A	τ 2A	τ 2A
		residue	2	443	109	48	306	48	167	48	184	440
O	rosmarus		AD	GN	VN	NN	-E
Z	californianu		AD	GN	VN	NN	-E
N	schauinslan		AD	GN	VN	NN	-E
U	arctos		AD	GN	VN	NN	-E
M	putorius		AD	GN	VN	NN	-E
M	erminea		AD	GN	VN	NN	-E
C	lupus		AD	GN	VN	NN	-E
V	vulpes		AD	GN	VN	NN	-E
P	discolor		AD	GN	VN	NN	-E
R	aegyptiacus		AD	GN	VN	NN	-E
H	armiger		AD	GN	VN	NN	-E
E	fuscus		AD	GN	VN	NN	-E
M	brandtii		TE	GN	VN	NN	-E
M	lucifugus		TE	GN	VN	NN	-E
P	alecto		AD	GN	VN	NN	-E
C	cristata		AD	GN	VN	NN	-E
E	europaeus		AD	GN	VN	-N	-E
O	afer		AD	GN	VN	NN	-E
T	manatus		AD	GN	VN	NN	-E
C	asiatica		TD	GN	VN	NN	-E
L	africana		AD	GN	VN	NN	-E
D	novemcinct		AD	GN	VN	NN	-E
S	harrisii		AD	GN	VN	NN	-E
M	domestica		AD	GN	VN	NN	-E
V	ursinus		AD	GN	VN	NN	-E
P	cinereus		AD	GN	VN	NN	-E
O	anatinus		AD	GN	VN	NN	-E
A	chrysaetos		AD	GN	VN	NN	AG

Correlated pairs

Genus	species	protein	τ 2A	τ 2A	τ 2A	τ 2A	τ 2A
		residue	2	443	109	48	306	48	167	48	184	440
A	platyrhyncho		AD	GN	VN	NN	AG
N	nippon		AD	GN	VN	NN	AG
F	cherrug		AD	GN	VN	NN	AG
C	vociferus		AD	GN	VN	NN	AG
S	camelus		AD	GN	VN	NN	AG
A	fulgula		AD	GN	VN	NN	AG
N	perdicaria		AD	GN	VN	NN	AG
C	canorus		-D	GN	VN	NN	AG
P	filicauda		-D	GN	VN	NN	AG
N	chrysocepha		-D	GN	VN	NN	AG
P	major		-D	GN	VN	NN	AG
T	guttata		-D	GN	VN	NN	AG
L	striata		-D	GN	VN	NN	AG
G	gallus		AD	GN	VN	NN	AG
C	coturnix		AD	GN	VN	NN	AG
P	humilis		-D	GN	VN	NN	AG
C	anna		-D	GN	VN	NN	AG
T	guttatus		AD	GN	VN	NN	AG
P	muralis		AD	GN	VN	NN	AG
A	carolinensis		AD	GS	VS	NS	AG
P	vitticeps		AD	VN	IN	SN	AG
T	elegans		AD	VS	IS	SS	AG
P	mucrosqua		AD	VN	IN	SN	AG
G	evgoodei		TD	GN	VN	NN	AG
C	mydas		AD	GN	VN	NN	AG

Supp. Fig. 1C



Supp. Fig. 1D

Supp. Fig. 2A

tau β-synuclein — Correlated pairs

Genus	species	protein / residue	τ 430 – β 3	τ 363 – β 88	τ 208 – β 4	τ 229 – β 4	τ 267 – β 4
		Z-score	5.6	4.5	3.9	3.9	3.9
H	sapiens		DV	VE	SF	VF	KF
P	troglodytes		DV	VE	SF	VF	KF
P	paniscus		DV	VE	SF	VF	KF
G	gorilla		DV	VE	SF	VF	KF
P	abelii		DV	VE	SF	VF	KF
H	moloch		DV	VE	SF	VF	KF
N	leucogenys		DV	VE	SF	VF	KF
P	anubis		DV	VE	SF	VF	KF
M	leucophaeus		DV	VE	SF	VF	KF
C	atys		DV	VE	SF	VF	KF
M	nemestrina		DV	VE	SF	VF	KF
M	mulatta		DV	VE	SF	VF	KF
M	fascicularis		DV	VE	SF	VF	KF
C	sabaeus		DV	VE	SF	VF	KF
T	gelada		DV	VE	SF	VF	KF
P	tephrosceles		DV	VE	SF	VF	KF
R	bieti		DV	VE	SF	VF	KF
R	roxellana		DV	VE	SF	VF	KF
C	capucinus		DV	VE	SF	VF	KF
S	boliviensis		DV	VE	SF	VF	KF
S	apella		DV	VE	SF	VF	KF
C	jacchus		DV	VE	SF	VF	KF
A	nancymaae		DV	VE	SF	VF	KF
P	coquereli		DV	VE	SF	VF	KF
M	murinus		DV	VE	SF	VF	KF
O	garnettii		DV	VE	SF	VF	KF
N	galili		DV	VE	SF	VF	KF
D	ordii		DV	VE	SF	VF	KF
J	jaculus		DV	VE	SF	VF	KF
M	flaviventris		DV	VE	SF	VF	KF
P	maniculatus		DV	VE	SF	VF	KF
M	ochrogaster		DV	VE	SF	VF	KF
M	marmota		DV	VE	SF	VF	KF
M	unguiculatus		DV	VE	SF	VF	KF
H	glaber		DV	VE	SF	VF	KF
C	griseus		DV	VE	SF	VF	KF
M	auratus		DV	VE	SF	VF	KF
R	norvegicus		DV	VE	SF	VF	KF
M	pahari		DV	VE	SF	VF	KF
M	caroli		DV	VE	SF	VF	KF
M	musculus		DV	VE	SF	VF	KF

Correlated pairs

Genus	species	protein / residue	τ 430 – β 3	τ 363 – β 88	τ 208 – β 4	τ 229 – β 4	τ 267 – β 4
I	tridecemline		DV	VE	SF	VF	KF
C	lanigera		DV	VE	SF	VF	KF
P	leucopus		DV	VE	SF	VF	KF
C	porcellus		DV	VE	SF	VF	KF
F	damarensis		DV	VE	SF	VF	KF
O	degus		DV	VE	SF	VF	KF
O	princeps		DV	VE	SF	VF	KF
O	cuniculus		DV	VE	SF	VF	KF
S	scrofa		DV	VE	SF	VF	KF
C	hircus		DV	VE	SF	VF	KF
O	aries		DV	VE	SF	VF	KF
O	virginianus		DV	VE	SF	VF	KF
B	taurus		DV	VE	SF	VF	KF
B	bison		DV	VE	SF	VF	KF
B	mutus		DV	VE	SF	VF	KF
C	ferus		DV	VE	SF	VF	KF
C	dromedarius		DV	VE	SF	VF	KF
B	acutorostrata		DV	VE	SF	VF	KF
L	obliquidens		DV	VE	SF	VF	KF
G	melas		DV	VE	SF	VF	KF
O	orca		DV	VE	SF	VF	KF
P	sinus		DV	VE	SF	VF	KF
N	asiaeoriental		DV	VE	SF	VF	KF
D	leucas		DV	VE	SF	VF	KF
M	monoceros		DV	VE	SF	VF	KF
L	vexillifer		DV	VE	SF	VF	KF
C	simum		DV	VE	SF	VF	KF
E	asinus		DV	VE	SF	VF	KF
E	caballus		DV	VE	SF	VF	KF
P	pardus		DV	VE	SF	VF	KF
L	canadensis		DV	VE	SF	VF	KF
L	pardinus		DV	VE	SF	VF	KF
F	catus		DV	VE	SF	VF	KF
A	jubatus		DV	VE	SF	VF	KF
P	vitulina		DV	VE	SF	VF	KF
O	rosmarus		DV	VE	SF	VF	KF
Z	californianu		DV	VE	SF	VF	KF
N	schauinslan		DV	VE	SF	VF	KF
U	arctos		DV	VE	SF	VF	KF
A	melanoleuc		DV	VE	SF	VF	KF
M	putorius		DV	VE	SF	VF	KF

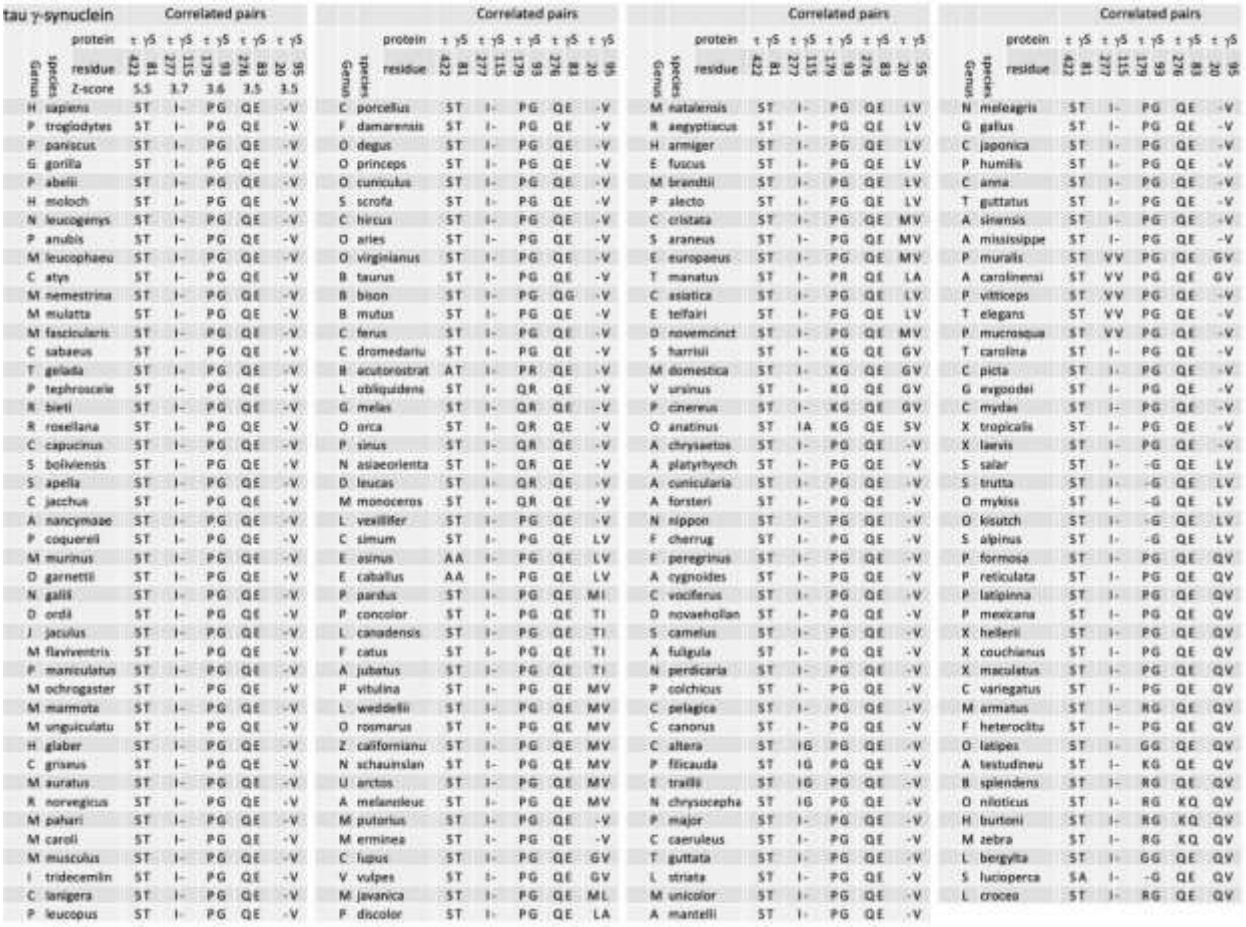
Correlated pairs

Genus	species	protein / residue	τ 430 – β 3	τ 363 – β 88	τ 208 – β 4	τ 229 – β 4	τ 267 – β 4
M	erminea		DV	VE	SF	VF	KF
C	lupus		DV	VE	SF	VF	KF
V	vulpes		DV	VE	SF	VF	KF
M	javanica		DV	VE	SF	VF	KF
P	discolor		DV	VE	SF	VF	KF
M	natalensis		DV	VE	SF	VF	KF
R	aegyptiacus		DV	VE	SF	VF	KF
H	armiger		DV	VE	SF	VF	KF
E	fuscus		DV	VE	SF	VF	KF
M	brandtii		DV	VE	SF	VF	KF
M	lucifugus		DV	VE	SF	VF	KF
P	alecto		DV	VE	SF	VF	KF
C	cristata		DV	VE	SF	VF	KF
S	araneus		DV	VE	SF	VF	KF
E	europaeus		DV	VE	SF	VF	KF
O	afer		EM	VE	SF	VF	KF
T	manatus		EM	VE	SF	VF	KF
C	asiatica		EM	VE	SF	VF	KF
E	telfairi		EM	VE	SF	VF	KF
D	novemcinct		DM	VE	SF	VF	KF
S	harrisii		DM	VE	SF	VF	KF
V	ursinus		DM	VE	SF	VF	KF
P	cinereus		DM	VE	SF	VF	KF
O	anatinus		DM	ID	SF	VF	KF
A	chrysaetos		DV	VE	SF	VF	KF
D	novaehollan		DV	VE	SF	VF	KF
A	fulgula		DV	VE	SF	VF	KF
N	perdicaria		DV	VE	SF	VF	KF
P	colchicus		DV	VE	SF	VF	KF
P	fasciata		DV	VE	SF	VF	KF
C	altera		DV	VE	SF	VF	KF
P	filicauda		DV	VE	SF	VF	KF
E	traillii		DV	VE	SF	VF	KF
N	chrysocepha		DV	VE	SF	VF	KF
T	guttata		DV	VE	SF	VF	KF
L	striata		DV	VE	SF	VF	KF
N	meleagris		DV	VE	SF	VF	KF
G	gallus		DV	VE	SF	VF	KF
C	japonica		DV	VE	SF	VF	KF
P	humilis		DV	VE	SF	VF	KF
C	anna		DV	VE	SF	VF	KF

Correlated pairs

Genus	species	protein / residue	τ 430 – β 3	τ 363 – β 88	τ 208 – β 4	τ 229 – β 4	τ 267 – β 4
P	muralis		DA	MD	SF	VF	KF
A	carolinensis		DV	ME	SF	VF	KF
P	vitticeps		DV	VE	SF	VF	KF
T	elegans		DA	ID	SF	VF	KF
T	sirtalis		DA	ID	SF	VF	KF
P	mucrosqua		DV	VE	SF	VF	KF
T	carolina		DA	IE	SF	VF	KF
C	picta		DA	VE	SF	VF	KF
G	evgoodei		DA	VE	SF	VF	KF
C	mydas		DA	VE	SF	VF	KF
X	tropicalis		DV	TE	GL	IL	RL
X	laevis		DV	VE	GL	IL	RL
S	salar		DV	VE	SF	VF	KF
S	trutta		DV	VE	SF	VF	KF
O	mykiss		DV	VE	SF	VF	KF
O	kisutch		DV	VE	SF	VF	KF
P	formosa		DV	VE	SF	VF	KF
P	reticulata		DV	VE	SF	VF	KF
P	latipinna		DV	VE	SF	VF	KF
P	mexicana		DV	VE	SF	VF	KF
X	helleri		DV	VE	SF	VF	KF
X	couchianus		DV	VE	SF	VF	KF
X	maculatus		DV	VE	SF	VF	KF
C	variegatus		DV	VE	SF	VF	KF
M	armatus		DV	VE	SF	VF	KF
F	heterocitus		DV	VE	SF	VF	KF
O	latipes		DV	VD	SF	VF	KF
A	testudineus		DV	VE	SF	VF	KF
B	splendens		DV	VE	SF	VF	KF
O	niloticus		DV	VE	SF	VF	KF
H	burtoni		DV	TE	SF	VF	KF
M	zebra		DV	IE	SF	VF	KF
N	brichardi		DV	VE	SF	VF	KF
L	bergylta		DV	VE	SF	VF	KF
A	ocellatus		DV	VE	SF	VF	KF
C	gobio		DV	VE	SF	VF	KF
S	lucioperca		DV	VE	SF	VF	KF
L	crocea		DV	VE	SF	VF	KF
S	aurata		DV	VE	SF	VF	KF

Supp. Fig. 2B



tau γ-synuclein

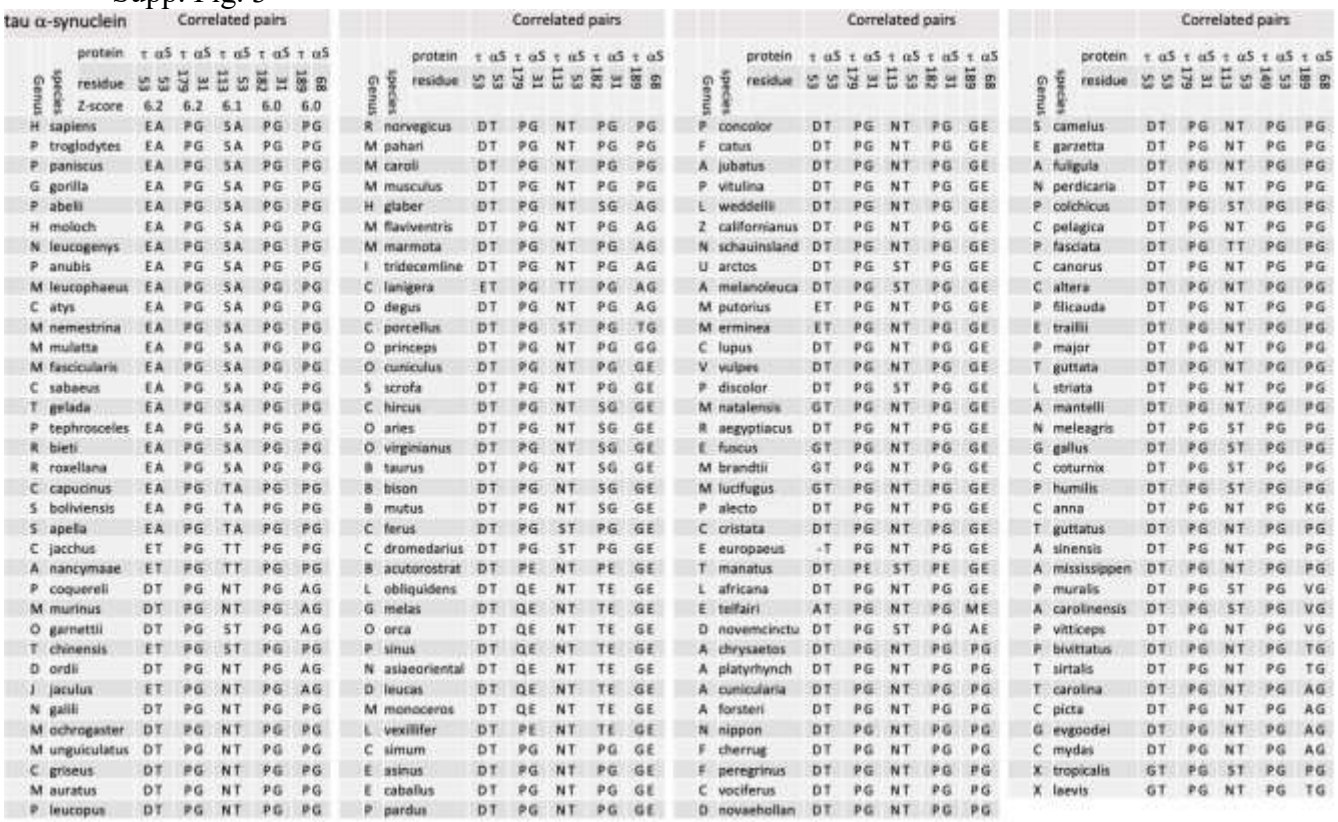
Genus	species	protein	τ γS 422	τ γS 277	τ γS 115	τ γS 179	τ γS 93	τ γS 276	τ γS 83	τ γS 20	τ γS 95
		residue	81								
		Z-score	5.5	3.7		3.6		3.5		3.5	
H	sapiens		ST	I-		PG		QE		-V	
P	troglodytes		ST	I-		PG		QE		-V	
P	paniscus		ST	I-		PG		QE		-V	
G	gorilla		ST	I-		PG		QE		-V	
P	abelii		ST	I-		PG		QE		-V	
H	moloch		ST	I-		PG		QE		-V	
N	leucogenys		ST	I-		PG		QE		-V	
P	anubis		ST	I-		PG		QE		-V	
M	leucophaeu		ST	I-		PG		QE		-V	
C	atys		ST	I-		PG		QE		-V	
M	nemestrina		ST	I-		PG		QE		-V	
M	mulatta		ST	I-		PG		QE		-V	
M	fascicularis		ST	I-		PG		QE		-V	
C	sabaeus		ST	I-		PG		QE		-V	
T	gelada		ST	I-		PG		QE		-V	
P	tephroscele		ST	I-		PG		QE		-V	
R	bieti		ST	I-		PG		QE		-V	
R	roxellana		ST	I-		PG		QE		-V	
C	capucinus		ST	I-		PG		QE		-V	
S	boliviensis		ST	I-		PG		QE		-V	
S	apella		ST	I-		PG		QE		-V	
C	jacchus		ST	I-		PG		QE		-V	
A	nancymaae		ST	I-		PG		QE		-V	
P	coquerel		ST	I-		PG		QE		-V	
M	murinus		ST	I-		PG		QE		-V	
O	garnettii		ST	I-		PG		QE		-V	
N	gallii		ST	I-		PG		QE		-V	
O	ordii		ST	I-		PG		QE		-V	
J	jaculus		ST	I-		PG		QE		-V	
M	flaviventris		ST	I-		PG		QE		-V	
P	maniculatus		ST	I-		PG		QE		-V	
M	ochrogaster		ST	I-		PG		QE		-V	
M	marmota		ST	I-		PG		QE		-V	
M	unguiculatu		ST	I-		PG		QE		-V	
H	glaber		ST	I-		PG		QE		-V	
C	griseus		ST	I-		PG		QE		-V	
M	auratus		ST	I-		PG		QE		-V	
R	norvegicus		ST	I-		PG		QE		-V	
M	pahari		ST	I-		PG		QE		-V	
M	caroli		ST	I-		PG		QE		-V	
M	musculus		ST	I-		PG		QE		-V	
I	tridecemlin		ST	I-		PG		QE		-V	
C	lanigera		ST	I-		PG		QE		-V	
P	leucopus		ST	I-		PG		QE		-V	

Genus	species	protein	τ γS 422	τ γS 81	τ γS 277	τ γS 115	τ γS 179	τ γS 93	τ γS 276	τ γS 83	τ γS 20	τ γS 95
		residue										
C	porcellus		ST	I-			PG		QE		-V	
F	damarensis		ST	I-			PG		QE		-V	
O	degus		ST	I-			PG		QE		-V	
O	princeps		ST	I-			PG		QE		-V	
O	cuniculus		ST	I-			PG		QE		-V	
S	scrofa		ST	I-			PG		QE		-V	
C	hircus		ST	I-			PG		QE		-V	
O	aries		ST	I-			PG		QE		-V	
O	virginianus		ST	I-			PG		QE		-V	
B	taurus		ST	I-			PG		QE		-V	
B	bison		ST	I-			PG		QG		-V	
B	mutus		ST	I-			PG		QE		-V	
C	ferus		ST	I-			PG		QE		-V	
C	dromedariu		ST	I-			PG		QE		-V	
B	acutorostrat		AT	I-			PR		QE		-V	
L	obliquidens		ST	I-			QR		QE		-V	
G	melas		ST	I-			QR		QE		-V	
O	orca		ST	I-			QR		QE		-V	
P	sinus		ST	I-			QR		QE		-V	
N	asiaeorienta		ST	I-			QR		QE		-V	
D	leucas		ST	I-			QR		QE		-V	
M	monoceros		ST	I-			QR		QE		-V	
L	vexillifer		ST	I-			PG		QE		-V	
S	simum		ST	I-			PG		QE		LV	
E	asinus		AA	I-			PG		QE		LV	
E	caballus		AA	I-			PG		QE		LV	
P	pardus		ST	I-			PG		QE		MI	
P	concolor		ST	I-			PG		QE		TI	
L	canadensis		ST	I-			PG		QE		TI	
F	catus		ST	I-			PG		QE		TI	
A	jubatus		ST	I-			PG		QE		TI	
P	vitulina		ST	I-			PG		QE		MV	
L	weddellii		ST	I-			PG		QE		MV	
O	rosmarus		ST	I-			PG		QE		MV	
Z	californianu		ST	I-			PG		QE		MV	
N	schauinslan		ST	I-			PG		QE		MV	
U	arctos		ST	I-			PG		QE		MV	
A	melanoleuc		ST	I-			PG		QE		MV	
M	putorius		ST	I-			PG		QE		-V	
M	erminea		ST	I-			PG		QE		-V	
C	lupus		ST	I-			PG		QE		GV	
V	vulpes		ST	I-			PG		QE		GV	
M	javanica		ST	I-			PG		QE		ML	
F	discolor		ST	I-			PG		QE		LA	

Genus	species	protein	τ γS 422	τ γS 81	τ γS 277	τ γS 115	τ γS 179	τ γS 93	τ γS 276	τ γS 83	τ γS 20	τ γS 95
		residue										
M	natalensis		ST	I-			PG		QE		LV	
R	aegyptiacus		ST	I-			PG		QE		LV	
H	armiger		ST	I-			PG		QE		LV	
E	fuscus		ST	I-			PG		QE		LV	
M	brandtii		ST	I-			PG		QE		LV	
P	alecto		ST	I-			PG		QE		LV	
C	cristata		ST	I-			PG		QE		MV	
S	araneus		ST	I-			PG		QE		MV	
E	europaeus		ST	I-			PG		QE		MV	
T	manatus		ST	I-			PR		QE		LA	
C	asiatica		ST	I-			PG		QE		LV	
E	telfairi		ST	I-			PG		QE		LV	
D	novemcinct		ST	I-			PG		QE		MV	
S	harrisii		ST	I-			KG		QE		GV	
M	domestica		ST	I-			KG		QE		GV	
V	ursinus		ST	I-			KG		QE		GV	
P	cinereus		ST	I-			KG		QE		GV	
O	anatinus		ST	IA			KG		QE		SV	
A	chrysaetos		ST	I-			PG		QE		-V	
A	platyrhynch		ST	I-			PG		QE		-V	
A	cunicularia		ST	I-			PG		QE		-V	
A	forsteri		ST	I-			PG		QE		-V	
N	nippon		ST	I-			PG		QE		-V	
F	cherrug		ST	I-			PG		QE		-V	
F	peregrinus		ST	I-			PG		QE		-V	
A	cygnoides		ST	I-			PG		QE		-V	
C	vociferus		ST	I-			PG		QE		-V	
D	novaehollan		ST	I-			PG		QE		-V	
S	camelus		ST	I-			PG		QE		-V	
A	fuligula		ST	I-			PG		QE		-V	
N	perdicaria		ST	I-			PG		QE		-V	
P	colchicus		ST	I-			PG		QE		-V	
C	pelagica		ST	I-			PG		QE		-V	
C	canorus		ST	I-			PG		QE		-V	
C	altera		ST	IG			PG		QE		-V	
P	filicauda		ST	IG			PG		QE		-V	
E	traillii		ST	IG			PG		QE		-V	
N	chrysocepha		ST	IG			PG		QE		-V	
P	major		ST	I-			PG		QE		-V	
C	caeruleus		ST	I-			PG		QE		-V	
T	guttata		ST	I-			PG		QE		-V	
L	striata		ST	I-			PG		QE		-V	
M	unicolor		ST	I-			PG		QE		-V	
A	mantelli		ST	I-			PG		QE		-V	

Genus	species	protein	τ γS 422	τ γS 81	τ γS 277	τ γS 115	τ γS 179	τ γS 93	τ γS 276	τ γS 83	τ γS 20	τ γS 95
		residue										
N	meleagris		ST	I-			PG		QE		-V	
G	gallus		ST	I-			PG		QE		-V	
C	japonica		ST	I-			PG		QE		-V	
P	humilis		ST	I-			PG		QE		-V	
C	anna		ST	I-			PG		QE		-V	
T	guttatus		ST	I-			PG		QE		-V	
A	sinensis		ST	I-			PG		QE		-V	
A	mississippe		ST	I-			PG		QE		-V	
P	muralis		ST	VV			PG		QE		GV	
A	carolinensi		ST	VV			PG		QE		GV	
P	vitticeps		ST	VV			PG		QE		-V	
T	elegans		ST	VV			PG		QE		-V	
P	mucrosqua		ST	VV			PG		QE		-V	
T	carolina		ST	I-			PG		QE		-V	
C	picta		ST	I-			PG		QE		-V	
G	evgoodei		ST	I-			PG		QE		-V	
C	mydas		ST	I-			PG		QE		-V	
X	tropicalis		ST	I-			PG		QE		-V	
X	laevis		ST	I-			PG		QE		-V	
S	salar		ST	I-			-G		QE		LV	
S	trutta		ST	I-			-G		QE		LV	
O	mykiss		ST	I-			-G		QE		LV	
O	kisutch		ST	I-			-G		QE		LV	
S	alpinus		ST	I-			-G		QE		LV	
P	formosa		ST	I-			PG		QE		QV	
P	reticulata		ST	I-			PG		QE		QV	
P	latipinna		ST	I-			PG		QE		QV	
P	mexicana		ST	I-			PG		QE		QV	
X	helleri		ST	I-			PG		QE		QV	
X	couchianus		ST	I-			PG		QE		QV	
X	maculatus		ST	I-			PG		QE		QV	
C	variegatus		ST	I-			PG		QE		QV	
M	armatus		ST	I-			RG		QE		QV	
F	heteroclitu		ST	I-			PG		QE		QV	
O	latipes		ST	I-			GG		QE		QV	
A	testudineu		ST	I-			KG		QE		QV	
B	splendens		ST	I-			RG		QE		QV	
O	niloticus		ST	I-			RG		KQ		QV	
H	burtoni		ST	I-			RG		KQ		QV	
M	zebra		ST	I-			RG		KQ		QV	
L	bergylta		ST	I-			GG		QE		QV	
S	lucioperca		SA	I-			-G		QE		QV	
L	croceo		ST	I-			RG		QE		QV	

Supp. Fig. 3



tau α-synuclein			Correlated pairs									
		protein	τ	αS	τ	αS	τ	αS	τ	αS	τ	αS
Genus	species	residue	53	53	179	31	113	53	182	31	189	68
		Z-score	6.2	6.2	6.1	6.0	6.0					
H	sapiens		EA	PG	SA	PG	PG					
P	troglodytes		EA	PG	SA	PG	PG					
P	paniscus		EA	PG	SA	PG	PG					
G	gorilla		EA	PG	SA	PG	PG					
P	abelii		EA	PG	SA	PG	PG					
H	moloch		EA	PG	SA	PG	PG					
N	leucogenys		EA	PG	SA	PG	PG					
P	anubis		EA	PG	SA	PG	PG					
M	leucophaeus		EA	PG	SA	PG	PG					
C	atys		EA	PG	SA	PG	PG					
M	nemestrina		EA	PG	SA	PG	PG					
M	mulatta		EA	PG	SA	PG	PG					
M	fascicularis		EA	PG	SA	PG	PG					
C	sabaeus		EA	PG	SA	PG	PG					
T	gelada		EA	PG	SA	PG	PG					
P	tephrosceles		EA	PG	SA	PG	PG					
R	bieti		EA	PG	SA	PG	PG					
R	roxellana		EA	PG	SA	PG	PG					
C	capucinus		EA	PG	TA	PG	PG					
S	boliviensis		EA	PG	TA	PG	PG					
S	apella		EA	PG	TA	PG	PG					
C	jacchus		ET	PG	TT	PG	PG					
A	nancymaae		ET	PG	TT	PG	PG					
P	coquereli		DT	PG	NT	PG	AG					
M	murinus		DT	PG	NT	PG	AG					
O	garnettii		DT	PG	ST	PG	AG					
T	chinensis		ET	PG	ST	PG	PG					
D	ordii		DT	PG	NT	PG	AG					
J	jaculus		ET	PG	NT	PG	AG					
N	galili		DT	PG	NT	PG	PG					
M	ochrogaster		DT	PG	NT	PG	PG					
M	unguiculatus		DT	PG	NT	PG	PG					
C	griseus		DT	PG	NT	PG	PG					
M	auratus		DT	PG	NT	PG	PG					
P	leucopus		DT	PG	NT	PG	PG					

			Correlated pairs									
		protein	τ	αS	τ	αS	τ	αS	τ	αS	τ	αS
Genus	species	residue	53	53	179	31	113	53	182	31	189	68
R	norvegicus		DT	PG	NT	PG	PG					
M	pahari		DT	PG	NT	PG	PG					
M	caroli		DT	PG	NT	PG	PG					
M	musculus		DT	PG	NT	PG	PG					
H	glaber		DT	PG	NT	SG	AG					
M	flaviventris		DT	PG	NT	PG	AG					
M	marmota		DT	PG	NT	PG	AG					
I	tridecemline		DT	PG	NT	PG	AG					
C	lanigera		ET	PG	TT	PG	AG					
O	degus		DT	PG	NT	PG	AG					
C	porcellus		DT	PG	ST	PG	TG					
O	princeps		DT	PG	NT	PG	GG					
O	cuniculus		DT	PG	NT	PG	GE					
S	scrofa		DT	PG	NT	PG	GE					
C	hircus		DT	PG	NT	SG	GE					
O	aries		DT	PG	NT	SG	GE					
O	virginianus		DT	PG	NT	SG	GE					
B	taurus		DT	PG	NT	SG	GE					
B	bison		DT	PG	NT	SG	GE					
B	mutus		DT	PG	NT	SG	GE					
C	ferus		DT	PG	ST	PG	GE					
C	dromedarius		DT	PG	ST	PG	GE					
B	acutorostrat		DT	PE	NT	PE	GE					
L	obliquidens		DT	QE	NT	TE	GE					
G	melas		DT	QE	NT	TE	GE					
O	orca		DT	QE	NT	TE	GE					
P	sinus		DT	QE	NT	TE	GE					
N	asiaeoriental		DT	QE	NT	TE	GE					
D	leucas		DT	QE	NT	TE	GE					
M	monoceros		DT	QE	NT	TE	GE					
L	vexillifer		DT	PE	NT	TE	GE					
C	simum		DT	PG	NT	PG	GE					
E	asinus		DT	PG	NT	PG	GE					
E	caballus		DT	PG	NT	PG	GE					
P	pardus		DT	PG	NT	PG	GE					

			Correlated pairs									
		protein	τ	αS	τ	αS	τ	αS	τ	αS	τ	αS
Genus	species	residue	53	53	179	31	113	53	182	31	189	68
P	concolor		DT	PG	NT	PG	GE					
F	catus		DT	PG	NT	PG	GE					
A	jubatus		DT	PG	NT	PG	GE					
P	vitulina		DT	PG	NT	PG	GE					
L	weddellii		DT	PG	NT	PG	GE					
Z	californianus		DT	PG	NT	PG	GE					
N	schauinsland		DT	PG	NT	PG	GE					
U	arctos		DT	PG	ST	PG	GE					
A	melanoleuca		DT	PG	ST	PG	GE					
M	putorius		ET	PG	NT	PG	GE					
M	erminea		ET	PG	NT	PG	GE					
C	lupus		DT	PG	NT	PG	GE					
V	vulpes		DT	PG	NT	PG	GE					
P	discolor		DT	PG	ST	PG	GE					
M	natalensis		GT	PG	NT	PG	GE					
R	aegyptiacus		DT	PG	NT	PG	GE					
E	fuscus		GT	PG	NT	PG	GE					
M	brandtii		GT	PG	NT	PG	GE					
M	lucifugus		GT	PG	NT	PG	GE					
P	alecto		DT	PG	NT	PG	GE					
C	cristata		DT	PG	NT	PG	GE					
E	europaeus		-T	PG	NT	PG	GE					
T	manatus		DT	PE	ST	PE	GE					
L	africana		DT	PG	NT	PG	GE					
E	telfairi		AT	PG	NT	PG	ME					
D	novemcinctu		DT	PG	ST	PG	AE					
A	chrysaetos		DT	PG	NT	PG	PG					
A	platyrhynch		DT	PG	NT	PG	PG					
A	cunicularia		DT	PG	NT	PG	PG					
A	forsteri		DT	PG	NT	PG	PG					
N	nippon		DT	PG	NT	PG	PG					
F	cherrug		DT	PG	NT	PG	PG					
F	peregrinus		DT	PG	NT	PG	PG					
C	vociferus		DT	PG	NT	PG	PG					
D	novaehollan		DT	PG	NT	PG	PG					

			Correlated pairs									
		protein	τ	αS	τ	αS	τ	αS	τ	αS	τ	αS
Genus	species	residue	53	53	179	31	113	53	149	53	189	68
S	camelus		DT	PG	NT	PG	PG					
E	garzetta		DT	PG	NT	PG	PG					
A	fuligula		DT	PG	NT	PG	PG					
N	perdicaria		DT	PG	NT	PG	PG					
P	colchicus		DT	PG	ST	PG	PG					
C	pelagica		DT	PG	NT	PG	PG					
P	fasciata		DT	PG	TT	PG	PG					
C	canorus		DT	PG	NT	PG	PG					
C	altera		DT	PG	NT	PG	PG					
P	filicauda		DT	PG	NT	PG	PG					
E	trailii		DT	PG	NT	PG	PG					
P	major		DT	PG	NT	PG	PG					
T	guttata		DT	PG	NT	PG	PG					
L	striata		DT	PG	NT	PG	PG					
A	mantelli		DT	PG	NT	PG	PG					
N	meleagris		DT	PG	ST	PG	PG					
G	gallus		DT	PG	ST	PG	PG					
C	coturnix		DT	PG	ST	PG	PG					
P	humilis		DT	PG	ST	PG	PG					
C	anna		DT	PG	NT	PG	KG					
T	guttatus		DT	PG	NT	PG	PG					
A	sinensis		DT	PG	NT	PG	PG					
A	mississippen		DT	PG	NT	PG	PG					
P	muralis		DT	PG	ST	PG	VG					
A	carolinensis		DT	PG	ST	PG	VG					
P	vitticeps		DT	PG	NT	PG	VG					
P	bivittatus		DT	PG	NT	PG	TG					
T	sirtalis		DT	PG	NT	PG	TG					
T	carolina		DT	PG	NT	PG	AG					
C	picta		DT	PG	NT	PG	AG					
G	evgoodei		DT	PG	NT	PG	AG					
C	mydas		DT	PG	NT	PG	AG					
X	tropicalis		GT	PG	ST	PG	PG					
X	laevis		GT	PG	NT	PG	TG					

Supp. Fig. 4A

α-syn. αIa-tub. Correlated pairs

Genus	species	protein	αS 1a	αS 1a	αS 1a	αS 1a	αS 1a
		residue	136	440	140	55	440	56	440	57	440
		Z-score	10.8	10.7	10.6	10.6	10.6
H	sapiens		YV	AV	VV	AV	EV
P	troglodytes		YV	AV	VV	AV	EV
G	gorilla		YV	AV	VV	AV	EV
P	abelii		YV	AV	VV	AV	EV
H	moloch		YV	AV	VV	AV	EV
N	leucogenys		YV	AV	VV	AV	EV
M	leucophaeu		YV	AV	VV	AV	EV
M	nemestrina		YV	AV	VV	AV	EV
M	mulatta		YV	AV	VV	AV	EV
M	fascicularis		YV	AV	VV	AV	EV
C	sabaeus		YV	AV	VV	AV	EV
P	tephroscele		YV	AV	VV	AV	EV
R	roxellana		YV	AV	VV	AV	EV
C	capucinus		YV	AV	VV	AV	EV
S	boliviensis		YV	AV	VV	AV	EV
S	apella		YV	AV	VV	AV	EV
C	jacchus		YV	AV	VV	AV	EV
A	nancymaae		YV	AV	VV	AV	EV
P	coquereli		YV	AV	VV	AV	EV
M	murinus		YV	AV	VV	AV	EV
O	garnettii		YV	AV	VV	AV	EV
D	ordii		YV	AV	VV	AV	EV
M	flaviventris		YV	AV	VV	AV	EV
M	marmota		YV	AV	VV	AV	EV
I	tridecemlin		YV	AV	VV	AV	EV
C	porcellus		YV	AV	VV	AV	EV
C	griseus		YV	AV	VV	AV	EV
P	leucopus		YV	AV	VV	AV	EV
R	norvergicus		YV	AV	VV	AV	EV
M	musculus		YV	AV	VV	AV	EV
O	cuniculus		YV	AV	VV	AV	EV
S	scrofa		YV	AV	VV	AV	EV

Correlated pairs

Genus	species	protein	αS 1a	αS 1a	αS 1a	αS 1a	αS 1a
		residue	136	440	140	55	440	56	440	57	440
C	hircus		YV	AV	VV	AV	EV
O	aries		YV	AV	VV	AV	EV
O	virginianus		YV	AV	VV	AV	EV
B	taurus		YV	AV	VV	AV	EV
B	mutus		YV	AV	VV	AV	EV
B	bubalis		YV	AV	VV	AV	EV
B	bison		YV	AV	VV	AV	EV
C	ferus		YV	AV	VV	AV	EV
L	obliquidens		YV	AV	VV	AV	EV
G	melas		YV	AV	VV	AV	EV
O	orca		YV	AV	VV	AV	EV
P	sinus		YV	AV	VV	AV	EV
O	leucas		YV	AV	VV	AV	EV
M	monoceros		YV	AV	VV	AV	EV
L	vexillifer		YV	AV	VV	AV	EV
C	simum		YV	AV	VV	AV	EV
E	asinus		YV	AV	VV	AV	EV
E	caballus		YV	AV	VV	AV	EV
P	pardus		YV	AV	VV	AV	EV
P	sinus		YV	AV	VV	AV	EV
O	leucas		YV	AV	VV	AV	EV
M	monoceros		YV	AV	VV	AV	EV
L	vexillifer		YV	AV	VV	AV	EV
C	simum		YV	AV	VV	AV	EV
E	asinus		YV	AV	VV	AV	EV
E	caballus		YV	AV	VV	AV	EV
P	pardus		YV	AV	VV	AV	EV
F	catus		YV	AV	VV	AV	EV
A	jubatus		YV	AV	VV	AV	EV
P	vitulina		YV	AV	VV	AV	EV
N	schauinslan		YV	AV	VV	AV	EV
U	arctos		YV	AV	VV	AV	EV
M	putorius		YV	AV	VV	AV	EV
M	erminea		YV	AV	VV	AV	EV
C	lupus		YV	AV	VV	AV	EV
P	discolor		YV	AV	VV	AV	EV
E	fuscus		YV	AV	VV	AV	EV
M	brandtii		YV	AV	VV	AV	EV
L	lucifugus		YV	AV	VV	AV	EV
R	aegyptiacus		YV	AV	VV	AV	EV

Correlated pairs

Genus	species	protein	αS 1a	αS 1a	αS 1a	αS 1a	αS 1a
		residue	136	440	140	55	440	56	440	57	440
L	africana		YV	AV	VV	AV	EV
D	novemcinct		YV	TV	VV	AV	EV
T	guttatus		YV	AV	VV	AV	EV
S	camelus		YV	AV	VV	AV	EV
C	coturnix		YV	AV	VV	AV	EV
G	gallus		YV	AV	VV	AV	EV
F	peregrinus		YV	AV	VV	AV	EV
C	anna		YV	AV	VV	AV	EV
C	livia		YV	AV	VV	AV	EV
E	garzetta		YV	AV	VV	AV	EV
P	filicauda		YV	AV	VV	AV	EV
C	altera		YV	AV	VV	AV	EV
F	albicollis		YV	AV	VV	AV	EV
C	moneduloid		YV	AV	VV	AV	EV
T	guttata		YV	AV	VV	AV	EV
P	humilis		YV	AV	VV	AV	EV
P	muralis		YV	AV	VV	AV	EV
A	carolinensis		YV	AV	VV	AV	EV
P	vitticeps		YV	AV	VV	AV	EV
P	bivittatus		YI	AI	VI	AI	EI
G	evgoodei		YV	AV	VV	AV	EV
X	tropicalis		YV	AV	VV	AV	EV
X	laevis		YV	AV	VV	AV	EV
N	parkeri		YV	AV	VV	AV	EV
R	bivittatum		YV	AV	VV	AV	EV
A	mexicanum		YV	AV	VV	AV	EV
L	chalumnae		YV	AV	VV	AV	EV
E	calabaricus		YV	AV	-V	-V	-V
P	kingsleyae		YV	-V	-V	-V	-V
S	formosus		YI	-I	-I	-I	-I
A	mexicanus		-I	-I	-I	-I	-I
P	nattereri		-I	-I	-I	-I	-I

Correlated pairs

Genus	species	protein	αS 1a	αS 1a	αS 1a	αS 1a	αS 1a
		residue	136	440	140	55	440	56	440	57	440
D	clupeoides		-I	-I	-I	-I	-I
E	electricus		-I	-I	-I	-I	-I
S	salar		YI	-I	-I	-I	-I
S	trutta		YI	-I	-I	-I	-I
O	mykiss		YI	-I	-I	-I	-I
O	kisutch		YI	-I	-I	-I	-I
P	formosa		-I	-I	-I	-I	-I
P	latipinna		-I	-I	-I	-I	-I
P	mexicana		-I	-I	-I	-I	-I
X	hellerii		-I	-I	-I	-I	-I
X	couchianus		-I	-I	-I	-I	-I
X	maculatus		-I	-I	-I	-I	-I
T	rubripes		-V	-V	-V	-V	-V
M	armatus		-I	-I	-I	-I	-I
O	latipes		-I	-I	-I	-I	-I
A	testudineus		-I	-I	-I	-I	-I
B	splendens		-I	-I	-I	-I	-I
O	niloticus		-I	-I	-I	-I	-I
H	burtoni		-I	-I	-I	-I	-I
M	zebra		-I	-I	-I	-I	-I
N	brichardi		-I	-I	-I	-I	-I
L	bergylta		-I	-I	-I	-I	-I
C	gobio		-V	-V	-V	-V	-V
S	lucioperca		-I	-I	-I	-I	-I
L	crocea		-I	-I	-I	-I	-I
S	aurata		-V	-V	-V	-V	-V
C	milii		YV	AV	VV	AV	EV
A	radiata		YI	AI	VI	AI	EI
R	typus		YI	AI	VI	AI	EI

Supp. Fig. 4B

α-syn βI-tub. Correlated pairs

Genus	species	protein	αS β1	αS β1	αS β1	αS β1	αS β1	αS β1
		residue	84	442	13	442	74	48	74	48	104	124
		Z-score	8.7	7.2	7.0	7.0	6.8
H	sapiens		GE	KE	VS	TS	EA
P	troglodytes		GE	KE	VS	TS	EA
G	gorilla		GE	KE	VS	TS	EA
P	abelii		GE	KE	VS	TS	EA
H	moloch		GE	KE	VS	TS	EA
N	leucogenys		GE	KE	VS	TS	EA
P	anubis		GE	KE	VS	TS	EA
M	leucophaeu		GE	KE	VS	TS	EA
C	atys		GE	KE	VS	TS	EA
M	nemestrina		GE	KE	VS	TS	EA
M	mulatta		GE	KE	VS	TS	EA
M	fascicularis		GE	KE	VS	TS	EA
C	sabaeus		GE	KE	VS	TS	EA
T	gelada		GE	KE	VS	TS	EA
P	tephroscele		GE	KE	VS	TS	EA
R	bieti		GE	KE	VS	TS	EA
R	roxellana		GE	KE	VS	TS	EA
S	boliviensis		GE	KE	VS	TS	EA
S	apella		GE	KE	VS	TS	EA
A	nancymaae		GE	KE	VS	TS	EA
P	coquereli		GE	KE	VS	TS	EA
M	murinus		GE	KE	VS	TS	EA
T	chinensis		GE	KE	VS	TS	EA
D	ordii		GE	KE	VS	TS	GA
J	jaculus		GE	KE	VS	TS	EA
M	flaviventris		GE	KE	VS	TS	EA
M	marmota		GE	KE	VS	TS	EA
I	tridecemlin		GE	KE	VS	TS	EA
C	lanigera		GE	KE	VS	TS	EA
C	porcellus		GE	KE	VS	TS	EA
H	glaber		GE	KE	VS	TS	EA
M	ochrogaster		GE	KE	VS	TS	EA
C	griseus		GE	KE	VS	TS	EA
P	maniculatus		GE	KE	VS	TS	EA
P	leucopus		GE	KE	VS	TS	EA
M	auratus		GE	KE	VS	TS	EA
R	norvergicus		GE	KE	VS	TS	EA
M	pahari		GE	KE	VS	TS	EA

Correlated pairs

Genus	species	protein	αS β1	αS β1	αS β1	αS β1	αS β1	αS β1
		residue	84	442	13	442	74	48	74	48	104	124
		Z-score										
M	caroli		GE	KE	VS	TS	EA
M	musculus		GE	KE	VS	TS	EA
O	princeps		GE	KE	VS	TS	EA
O	cuniculus		GE	KE	VS	TS	EA
S	scrofa		GE	KE	VS	TS	EA
C	hircus		GE	KE	VS	TS	EA
O	aries		GE	KE	VS	TS	EA
O	virginianus		GE	KE	VS	TS	EA
B	taurus		GE	KE	VS	TS	EA
B	mutus		GE	KE	VS	TS	EA
B	bubalis		GE	KE	VS	TS	EA
C	ferus		GE	KE	VS	TS	EA
C	dromedariu		GE	KE	VS	TS	EA
V	pacos		GE	KE	VS	TS	EA
B	acutorostrat		GE	KE	VS	TS	-A
L	obliquidens		GE	KE	VS	TS	-A
G	melas		GE	KE	VS	TS	-A
O	orca		GE	KE	VS	TS	DA
P	sinus		GE	KE	VS	TS	-A
N	asiaeorienta		GE	KE	VS	TS	-A
D	leucas		GE	KE	VS	TS	-A
M	monoceros		GE	KE	VS	TS	-A
L	vexillifer		GE	KE	VS	TS	DA
C	simum		GE	KE	VS	TS	EA
E	asinus		GE	KE	VS	TS	EA
E	caballus		GE	KE	VS	TS	EA
P	pardus		GE	KE	VS	TS	EA
P	concolor		GE	KE	VS	TS	EA
F	catus		GE	KE	VS	TS	EA
A	jubatus		GE	KE	VS	TS	EA
P	vitulina		GE	KE	VS	TS	EA
L	weddellii		GE	KE	VS	TS	EA
N	schauinslan		GE	KE	VS	TS	EA
U	arctos		GE	KE	VS	TS	EA
M	putorius		GE	KE	VS	TS	EA
M	erminea		GE	KE	VS	TS	EA
C	lupus		GE	KE	VS	TS	EA
V	vulpes		GE	KE	VS	TS	EA

Correlated pairs

Genus	species	protein	αS β1	αS β1	αS β1	αS β1	αS β1	αS β1
		residue	84	442	13	442	74	48	74	48	104	124
		Z-score										
P	discolor		GE	KE	VS	TS	EA
E	fuscus		GE	KE	VS	TS	EA
M	brandtii		GE	KE	VS	TS	EA
R	aegyptiacus		GE	KE	VS	TS	EA
P	alecto		GE	KE	VS	TS	EA
C	cristata		GE	KE	VS	TS	EA
E	telfairi		GE	KE	VS	TS	EA
T	manatus		GE	KE	VS	TS	EA
D	novemcinct		GE	KE	VS	TS	EA
N	perdicaria		GE	KE	VS	TS	EA
P	colchicus		GE	KE	VS	TS	EA
G	gallus		GE	KE	VS	TS	EA
A	cunicularia		GE	KE	VS	TS	EA
A	chrysaetos		GE	KE	VS	TS	EA
C	pelagica		GE	KE	VS	TS	EA
P	fasciata		GE	KE	VS	TS	EA
C	canorus		GE	KE	VS	TS	EA
M	undulatus		GE	KE	VS	TS	EA
E	garzetta		GE	KE	VS	TS	EA
P	filicauda		GE	KE	VS	TS	EA
C	moneduloid		GE	KE	VS	TS	EA
T	guttata		GE	KE	VS	TS	EA
L	striata		GE	KE	VS	TS	EA
P	humilis		GE	KE	VS	TS	EA
P	muralis		GE	KE	VS	TS	EA
A	carolinensis		GE	KE	VS	TS	DA
P	vitticeps		GE	KE	VS	TS	NA
P	bivittatus		GE	KE	VS	TS	EA
T	sirtalis		GE	KE	VS	TS	EA
T	carolina		GE	KE	VS	TS	EA
C	picta		GE	KE	VS	TS	EA
G	evgoodei		GE	KE	VS	TS	EA
X	tropicalis		GE	KE	VS	TS	EA
X	laevis		GE	KE	VS	TS	EA
R	bivittatum		GE	KE	VS	TS	EA
L	chalumnae		GE	KE	VS	TS	ES
E	calabaricus		GE	KE	VS	TS	EA

Correlated pairs

Genus	species	protein	αS β1	αS β1	αS β1	αS β1	αS β1	αS β1
		residue	84	442	13	442	74	48	74	48	104	124
		Z-score										
P	kingsleyae		GE	KE	VS	TS	EA
S	formosus		GE	KE	VS	TS	EA
A	mexicanus		GE	KE	VS	TS	DS
P	nattereri		GE	KE	VS	TS	DS
D	clupeoides		GE	KE	VS	TS	EA
S	salar		GE	KE	VS	TS	EA
S	trutta		GE	KE	VS	TS	EA
O	mykiss		GE	KE	VS	TS	EA
O	kisutch		GE	KE	VS	TS	EA
S	alpinus		GE	KE	VS	TS	EA
G	morhua		GE	KE	VS	TS	EA
P	formosa		GE	KE	VS	TS	EA
P	reticulata		GE	KE	VS	TS	ES
P	latipinna		GE	KE	VS	TS	ES
P	mexicana		GE	KE	VS	TS	ES
X	hellerii		GE	KE	VS	TS	EA
X	couchianus		GE	KE	VS	TS	EA
X	maculatus		GE	KE	VS	TS	EA
C	variegatus		GE	KE	VS	TS	ES
T	rubripes		SD	KD	VS	TS	DS
M	armatus		GE	KE	VS	TS	NS
O	latipes		GE	KE	VS	TS	DS
A	testudineus		GE	KE	VS	TS	DS
B	splendens		GE	KE	VS	TS	ES
O	niloticus		GE	KE	VS	TS	DS
H	burtoni		GE	KE	VS	TS	DS
M	zebra		GE	KE	VS	TS	DS
N	brichardi		GE	KE	VS	TS	DS
L	bergylta		SD	KD	VS	TS	ES
A	ocellatus		GD	RD	VS	TS	DS
C	gobio		GE	KE	VS	TS	DA
S	lucioperca		GD	RD	VS	TS	DS
L	crocea		SD	KD	VS	TS	DS
S	aurata		GD	KD	VS	TS	DS
C	milii		GD	KD	MN	SN	EA
R	typus		GQ	KQ	MN	SN	EA

Supp. Fig. 4C

α-syn. βIIa-tub. Correlated pairs

Genus	species	protein	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a
		residue	100	443	64	440	101	440	114	440	99	55
		Z-score	8.5	8.4	8.4	8.4	8.4	8.4				
H	sapiens		LD	TE	-E	-E	QA
P	troglodytes		LD	TE	-E	-E	QA
P	paniscus		LD	TE	-E	-E	QA
G	gorilla		LD	TE	-E	-E	QA
P	abelii		LD	TE	-E	-E	QA
N	leucogenys		LD	TE	-E	-E	QA
P	anubis		LD	TE	-E	-E	QA
M	leucophaeu		LD	TE	-E	-E	QT
C	atys		LD	TE	-E	-E	QA
M	nemestrina		LD	TE	-E	-E	QA
M	mulatta		LD	TE	-E	-E	QA
M	fascicularis		LD	TE	-E	-E	QA
C	sabaeus		LD	TE	-E	-E	QA
T	gelada		LD	TE	-E	-E	QA
R	roxellana		LD	TE	-E	-E	QA
C	capucinus		LD	TE	-E	-E	HT
S	boliviensis		LD	TE	-E	-E	HA
S	apella		LD	TE	-E	-E	HT
C	jacchus		LD	TE	-E	-E	HT
M	murinus		FD	TE	-E	-E	QA
D	ordii		LD	TE	-E	-E	QA
J	jaculus		MD	TE	-E	-E	QT
M	marmota		LD	TE	-E	-E	QA
I	tridecemlin		LD	TE	-E	-E	QA
C	lanigera		LD	TE	-E	-E	QA
O	degus		LD	TE	-E	-E	QA
C	porcellus		LD	TE	-E	-E	QA

Correlated pairs

Genus	species	protein	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a
		residue	100	443	64	440	101	440	114	440	99	55
		Z-score										
N	gallí		-D	TE	-E	-E	-A
H	glaber		LD	TE	-E	-E	QT
M	ochrogaster		MD	TE	-E	-E	QA
C	griseus		LD	TE	-E	-E	QA
P	maniculatus		MD	TE	-E	-E	QA
P	leucopus		LD	TE	-E	-E	QA
M	auratus		TD	TE	-E	-E	KA
R	norvergicus		MD	TE	-E	-E	QA
M	musculus		MD	TE	-E	-E	QA
O	princeps		QD	TE	-E	-E	QA
O	cuniculus		QD	TE	-E	-E	QA
S	scrofa		LD	TE	-E	-E	QA
C	hircus		LD	TE	-E	-E	HA
O	aries		LD	TE	-E	-E	HA
B	taurus		MD	TE	-E	-E	HA
B	bubalis		LD	TE	-E	-E	HA
B	bison		MD	TE	-E	-E	HA
C	ferus		LD	TE	-E	-E	QA
C	dromedariu		LD	TE	-E	-E	RA
B	acutorostrat		LD	TE	-E	-E	QA
L	obliquidens		LD	TE	-E	-E	QA
O	orca		LD	TE	-E	-E	QA
P	sinus		LD	TE	-E	-E	QA
D	leucas		LD	TE	-E	-E	QA
M	monoceros		LD	TE	-E	-E	QA
L	vexillifer		LD	TE	-E	-E	QA
C	simum		LD	TE	-E	-E	QA

Correlated pairs

Genus	species	protein	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a
		residue	100	443	64	440	101	440	114	440	99	55
		Z-score										
E	caballus		LD	TE	-E	-E	HA
P	pardus		LD	TE	-E	-E	QA
F	catus		LD	TE	-E	-E	QA
A	jubatus		LD	TE	-E	-E	QA
P	vitulina		LD	TE	-E	-E	QA
L	weddellii		LD	TE	-E	-E	QA
N	schauinslan		LD	TE	-E	-E	QA
Z	californianu		LD	TE	-E	-E	QA
U	arctos		LD	TE	-E	-E	QA
M	putorius		LD	TE	-E	-E	QA
M	erminea		LD	TE	-E	-E	QA
C	lupus		LD	TE	-E	-E	QA
V	vulpes		LD	TE	-E	-E	QA
P	discolor		LD	TE	-E	-E	QA
E	fuscus		LD	TE	-E	-E	QA
M	brandtii		VE	TE	-E	-E	QA
M	lucifugus		VE	TE	-E	-E	QA
R	aegyptiacus		LD	TE	-E	-E	QA
P	alecto		LD	TE	-E	-E	QA
C	cristata		FD	TE	-E	-E	QA
E	europaeus		MD	TE	-E	-E	QA
E	telfairi		TE	TE	-E	-E	QT
T	manatus		MD	TE	-E	-E	QA
L	africana		MD	TE	-E	-E	QA
D	novemcinct		LD	TE	-E	-E	QA
N	perdicaria		LD	SG	QG	NG	QA
T	guttatus		LD	SG	QG	NG	QA

Correlated pairs

Genus	species	protein	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a	α5 2a
		residue	100	443	64	440	101	440	114	440	99	55
		Z-score										
S	camelus		LD	SG	QG	NG	QA
C	coturnix		LD	SG	QG	NG	QA
G	gallus		LD	SG	QG	NG	QA
A	platyrhynch		LD	SG	QG	NG	HA
A	fuligula		LD	SG	QG	NG	QA
A	chrysaetos		LD	SG	QG	NG	QA
F	cherrug		LD	SG	QG	NG	QA
C	anna		LD	SG	QG	NG	QA
C	livia		LD	SG	QG	NG	PA
C	vociferus		LD	SG	QG	NG	QA
N	nippon		LD	SG	QG	NG	QA
C	canorus		LD	SG	QG	NG	QA
M	undulatus		FD	SG	QG	NG	QA
P	filicauda		LD	SG	QG	NG	QA
F	albicollis		LD	SG	QG	NG	QA
C	moneduloid		LD	SG	QG	NG	QA
P	major		LD	SG	QG	NG	QA
T	guttata		LD	SG	QG	NG	QA
L	striata		LD	SG	QG	NG	QA
P	humilis		LD	SG	QG	NG	QA
Z	albicollis		LD	SG	QG	NG	QA
P	muralis		LD	SG	QG	NG	QA
A	carolinensis		LD	SG	QG	NG	QA
P	vitticeps		-D	SG	QG	NG	-A
G	evgoodei		LD	SG	QG	NG	QA
C	mydas		LD	SG	QG	NG	QA

Supp. Fig 4D

α-syn. βIIb-tub. Correlated pairs

Genus	species	protein	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b
		residue	43	443	64	440	103	440	101	440	121	440
		Z-score	9.6	8.4	8.3	8.3	8.3					
H	sapiens		KG	TE	-E	GE	DE
P	troglodytes		KG	TE	-E	GE	DE
P	paniscus		KG	TE	-E	GE	DE
G	gorilla		KG	TE	-E	GE	DE
P	abelii		KG	TE	-E	GE	DE
N	leucogenys		KG	TE	-E	GE	DE
P	anubis		KG	TE	-E	GE	DE
M	leucophaeu		KG	TE	-E	GE	DE
C	atys		KG	TE	-E	GE	DE
M	nemestrina		KG	TE	-E	GE	DE
M	mulatta		KG	TE	-E	GE	DE
M	fascicularis		KG	TE	-E	GE	DE
C	sabaeus		KG	TE	-E	GE	DE
T	gelada		KG	TE	-E	GE	DE
P	tephrosele		KG	TE	-E	GE	DE
R	roxellana		KG	TE	-E	GE	DE
C	capucinus		KG	TE	-E	SE	DE
S	boliviensis		KG	TE	-E	GE	DE
S	apella		KG	TE	-E	GE	DE
A	nancymaae		KG	TE	-E	GE	DE
M	murinus		KG	TE	-E	GE	DE
O	garnettii		KG	TE	-E	GE	DE
T	chinensis		KG	TE	-E	GE	DE
D	ordii		KG	TE	-E	GE	DE
J	jaculus		KG	TE	-E	GE	DE
M	flaviventris		KG	TE	-E	GE	DE
M	marmota		KG	TE	-E	GE	DE
I	tridecemlin		KG	TE	-E	GE	DE
C	lanigera		KG	TE	-E	GE	DE
C	porcellus		KG	TE	-E	GE	DE
N	gallí		KG	TE	-E	-E	DE
H	glaber		KG	TE	-E	GE	DE

Correlated pairs

Genus	species	protein	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b
		residue	43	443	64	440	103	440	101	440	121	440
M	ochrogaster		KG	TE	-E	GE	SE
C	griseus		KG	TE	-E	GE	GE
P	maniculatus		KG	TE	-E	GE	GE
P	leucopus		KG	TE	-E	GE	GE
R	norvergicus		KG	TE	-E	GE	SE
M	caroli		KG	TE	-E	GE	GE
M	musculus		KG	TE	-E	GE	GE
O	princeps		KG	TE	-E	GE	DE
O	cuniculus		KG	TE	-E	GE	DE
S	scrofa		KG	TE	-E	GE	DE
C	hircus		KG	TE	-E	GE	DE
O	aries		KG	TE	-E	GE	DE
O	virginianus		KG	TE	-E	GE	DE
B	taurus		KG	TE	-E	GE	DE
B	mutus		KG	TE	-E	GE	DE
B	bubalis		KG	TE	-E	GE	DE
C	ferus		KG	TE	-E	SE	DE
C	dromedariu		KG	TE	-E	SE	DE
B	acutorostrat		KG	TE	-E	GE	DE
L	obliquidens		KG	TE	-E	GE	DE
G	melas		KG	TE	-E	GE	DE
O	orca		KG	TE	-E	GE	DE
P	sinus		KG	TE	-E	GE	DE
N	asiaeorienta		KG	TE	-E	GE	DE
D	leucas		KG	TE	-E	GE	DE
M	monoceros		KG	TE	-E	GE	DE
L	vexillifer		KG	TE	-E	GE	DE
C	simum		KG	TE	-E	GE	DE
E	asinus		KG	TE	-E	GE	DE
E	caballus		KG	TE	-E	GE	DE
P	pardus		KG	TE	-E	GE	DE
F	catus		KG	TE	-E	GE	DE

Correlated pairs

Genus	species	protein	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b
		residue	43	443	64	440	102	440	101	440	121	440
A	jubatus		KG	TE	-E	GE	DE
P	vitulina		KG	TE	-E	GE	DE
L	weddellii		KG	TE	-E	GE	DE
N	schauinslan		KG	TE	-E	GE	DE
U	arctos		KG	TE	-E	GE	DE
A	melanoleuc		KG	TE	-E	GE	DE
M	erminea		KG	TE	-E	GE	DE
C	lupus		KG	TE	-E	GE	DE
P	discolor		KG	TE	-E	GE	DE
M	natalensis		KG	TE	-E	SE	DE
E	fuscus		RV	TE	-E	GE	DE
M	lucifugus		RG	TE	-E	GE	DE
R	aegyptiacus		KG	TE	-E	GE	DE
P	alecto		KG	TE	-E	GE	EE
E	europaeus		KG	TE	-E	GE	DE
E	telfairi		KG	TE	-E	GE	DE
E	edwardii		KG	TE	-E	GE	DE
T	manatus		KG	TE	-E	GE	DE
L	africana		KG	TE	-E	GE	DE
S	camelus		RE	SG	QG	AG	EG
P	colchicus		RE	SG	QG	AG	EG
G	gallus		RE	SG	QG	AG	EG
A	fuligula		RE	SG	QG	AG	EG
A	chrysaetos		RE	SG	QG	AG	EG
C	anna		RE	SG	QG	GG	EG
C	livia		RE	SG	QG	AG	EG
A	forsteri		RE	SG	QG	AG	EG
N	nippon		RE	SG	QG	AG	EG
E	trailli		RE	SG	QG	AG	EG
P	filicauda		RE	SG	QG	AG	EG
F	albicollis		RE	SG	QG	AG	EG
C	moneduloid		RE	SG	QG	AG	EG

Correlated pairs

Genus	species	protein	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b	α5 2b
		residue	43	443	64	440	102	440	101	440	121	440
T	guttata		RE	SG	QG	AG	EG
L	striata		RE	SG	QG	AG	EG
P	humilis		RE	SG	QG	AG	EG
A	sinensis		RE	SG	QG	AG	EG
P	muralis		KE	SG	QG	AG	EG
P	vitticeps		KE	SG	QG	-G	EG
P	bivittatus		KE	SG	QG	AG	EG
C	picta		RE	SG	QG	AG	DG
G	evgoodei		RE	SG	QG	AG	DG
X	tropicalis		KG	SE	-E	-E	DE
X	laevis		KG	SE	-E	-E	NE
N	parkeri		KG	SE	QE	GE	DE
R	bivittatum		KG	TE	QE	GE	NE
A	mexicanum		KG	SE	QE	AE	DE
L	chalumnae		KG	SE	EE	NE	AE
A	mexicanus		KG	S-	V-	T-	D-
P	nattereri		KG	S-	V-	T-	D-
S	salar		KG	S-	Q-	A-	D-
S	trutta		KG	S-	Q-	A-	D-
O	mykiss		KG	S-	Q-	A-	D-
O	kisutch		KG	S-	Q-	A-	D-
G	morhua		KG	S-	N-	A-	D-
P	reticulata		KG	S-	Q-	A-	E-
P	latipinna		KG	S-	Q-	A-	E-
X	hellerii		KG	S-	Q-	A-	E-
X	couchianus		KG	S-	Q-	A-	E-
X	maculatus		KG	S-	Q-	A-	E-
B	splendens		KG	S-	P-	A-	L-
C	milii		KG	SE	QE	VE	EE

Supp. Fig. 4E

α-syn. βIII-tub.

Genus	species	protein	αS B3	αS B3	αS B3	αS B3	αS B3	αS B3
		residue	64 449	102 449	101 449	94 449	43 449	
		Z-score	11.7	11.5	11.1	11.0	10.9	
H	sapiens		TP	-P	GP	FP	KP	
P	troglodytes		TP	-P	GP	FP	KP	
P	paniscus		TP	-P	GP	FP	KP	
G	gorilla		TP	-P	GP	FP	KP	
P	abelii		TP	-P	GP	FP	KP	
N	leucogenys		TP	-P	GP	FP	KP	
P	anubis		TP	-P	GP	FP	KP	
C	atys		TP	-P	GP	FP	KP	
M	fascicularis		TP	-P	GP	FP	KP	
C	sabaeus		TP	-P	GP	FP	KP	
T	gelada		TP	-P	GP	FP	KP	
P	tephroscele		TP	-P	GP	FP	KP	
R	bieti		TP	-P	GP	FP	KP	
R	roxellana		TP	-P	GP	FP	KP	
C	capucinus		TP	-P	SP	FP	KP	
S	boliviensis		TP	-P	GP	FP	KP	
C	jacchus		TP	-P	GP	FP	KP	
P	coquereli		TP	-P	GP	FP	KP	
O	garnettii		TP	-P	GP	FP	KP	
T	chinensis		TP	-P	GP	FP	KP	
D	ordii		TP	-P	GP	FP	KP	
J	jaculus		TP	-P	GP	FP	KP	
M	flaviventris		TP	-P	GP	FP	KP	
I	tridecemlin		TP	-P	GP	FP	KP	
C	lanigera		TP	-P	GP	FP	KP	
O	degus		TP	-P	GP	FP	KP	
C	porcellus		TP	-P	GP	FP	KP	
N	galili		TP	-P	-P	FP	KP	
H	glaber		TP	-P	GP	FP	KP	
M	ochrogaster		TP	-P	GP	FP	KP	
C	griseus		TP	-P	GP	FP	KP	
P	maniculatus		TP	-P	GP	FP	KP	

Genus	species	protein	αS B3	αS B3	αS B3	αS B3	αS B3	αS B3
		residue	64 449	102 449	101 449	94 449	43 449	
		Z-score						
P	leucopus		TP	-P	GP	FP	KP	
M	auratus		TP	-P	GP	FP	KP	
R	norvergicus		TP	-P	GP	FP	KP	
M	pahari		TP	-P	GP	FP	KP	
M	caroli		TP	-P	GP	FP	KP	
M	musculus		TP	-P	GP	FP	KP	
O	princeps		TP	-P	GP	FP	KP	
O	cuniculus		TP	-P	GP	FP	KP	
C	hircus		TP	-P	GP	FP	KP	
O	virginianus		TP	-P	GP	FP	KP	
B	taurus		TP	-P	GP	FP	KP	
B	bubalis		TP	-P	GP	FP	KP	
C	ferus		TP	-P	SP	FP	KP	
C	dromedariu		TP	-P	SP	FP	KP	
V	pacos		TP	-P	SP	FP	KP	
L	obliquidens		TP	-P	GP	FP	KP	
O	orca		TP	-P	GP	FP	KP	
P	sinus		TP	-P	GP	FP	KP	
N	asiaeorienta		TP	-P	GP	FP	KP	
D	leucas		TP	-P	GP	FP	KP	
M	monoceros		TP	-P	GP	FP	KP	
L	vexillifer		TP	-P	GP	FP	KP	
C	simum		TP	-P	GP	FP	KP	
E	asinus		TP	-P	GP	FP	KP	
E	caballus		TP	-P	GP	FP	KP	
P	pardus		TP	-P	GP	FP	KP	
P	concolor		TP	-P	GP	FP	KP	
A	jubatus		TP	-P	GP	FP	KP	
P	vitulina		TP	-P	GP	FP	KP	
L	weddellii		TP	-P	GP	FP	KP	
N	schauinslan		TP	-P	GP	FP	KP	
Z	californianu		TP	-P	GP	FP	KP	

Genus	species	protein	αS B3	αS B3	αS B3	αS B3	αS B3	αS B3
		residue	64 449	102 449	101 449	94 449	43 449	
		Z-score						
U	arctos		TP	-P	GP	FP	KP	
M	putorius		TP	-P	GP	FP	KP	
M	erminea		TP	-P	GP	FP	KP	
C	lupus		TP	-P	GP	FP	KP	
V	vulpes		TP	-P	GP	FP	KP	
P	discolor		TP	-P	GP	FP	KP	
E	fuscus		TP	-P	GP	FP	RP	
M	brandtii		TP	-P	GP	FP	RP	
M	lucifugus		TP	-P	GP	FP	RP	
R	aegyptiacus		TP	-P	GP	FP	KP	
E	europaeus		TP	-P	GP	FP	KP	
E	telfairi		TP	-P	GP	FP	KP	
E	edwardii		TP	-P	GP	FP	KP	
T	manatus		TP	-P	GP	FP	KP	
L	africana		TP	-P	GP	FP	KP	
N	perdicaria		SA	QA	AA	LA	RA	
S	camelus		SA	QA	AA	LA	RA	
N	meleagris		SA	QA	AA	LA	RA	
P	colchicus		SA	QA	AA	LA	RA	
G	gallus		SA	QA	AA	LA	RA	
A	platyrhynch		SA	QA	AA	LA	RA	
A	fuligula		SA	QA	AA	LA	RA	
A	chrysaetos		SA	QA	AA	LA	RA	
F	cherrug		SA	QA	AA	LA	RA	
C	anna		SA	QA	GA	LA	RA	
P	fasciata		SA	QA	AA	LA	RA	
C	vociferus		SA	QA	AA	LA	RA	
N	nippon		SA	QA	AA	LA	RA	
C	canorus		SA	QA	AA	LA	RA	
M	undulatus		ST	QT	AT	LT	RT	
E	traillii		SA	QA	AA	LA	RA	
P	filicauda		SA	QA	AA	LA	RA	

Genus	species	protein	αS B3	αS B3	αS B3	αS B3	αS B3	αS B3
		residue	449	102 449	101 449	449	43 449	
		Z-score	64			94		
C	altera		SA	QA	AA	LA	RA	
C	moneduloid		SA	QA	AA	LA	RA	
T	guttata		SA	QA	AA	LA	RA	
L	striata		SA	QA	AA	LA	RA	
A	mississippie		SA	QA	AA	LA	RA	
P	muralis		SA	QA	AA	FA	KA	
A	carolinensis		SG	QG	GG	FG	KG	
P	vitticeps		SA	QA	-A	FA	KA	
T	sirtalis		SA	QA	AA	FA	KA	
T	carolina		SA	QA	AA	LA	RA	
C	picta		SA	QA	AA	LA	RA	
G	evgoodei		SA	QA	AA	LA	RA	
C	mydas		SA	QA	AA	LA	RA	
X	tropicalis		S-	--	--	L-	K-	
X	laevis		S-	--	--	L-	K-	
N	parkeri		S-	Q-	G-	L-	K-	
R	bivittatum		TG	QG	GG	LG	KG	
A	mexicanum		S-	Q-	A-	L-	K-	
L	chalumnae		SQ	EQ	NQ	LQ	KQ	
E	calabaricus		SQ	QQ	GQ	LQ	KQ	
P	kingsleyae		SP	QP	DP	LP	KP	
S	formosus		SQ	QQ	SQ	LQ	KQ	
A	mexicanus		SQ	VQ	TQ	LQ	KQ	
P	nattereri		SQ	VQ	TQ	LQ	KQ	
E	electricus		SQ	TQ	PQ	LQ	KQ	
S	salar		SA	QA	AA	LA	KA	
S	trutta		SA	QA	AA	LA	KA	
O	mykiss		SA	QA	AA	LA	KA	
O	kisutch		SA	QA	AA	LA	KA	
S	alpinus		SQ	QQ	AQ	LQ	KQ	
C	milii		SP	QP	VP	LP	KP	
R	typus		SP	QP	VP	LP	RP	

Supp. Fig. 4F

α-syn. βIVa-tub.

Genus	species	protein	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a
		residue	12	35 10	55 5	35 58	35 59	35
		Z-score	8.1	7.6	7.4	7.4	7.4	
H	sapiens		KT	KT	MT	KT	TT	
P	troglodytes		KT	KT	MT	KT	TT	
P	paniscus		KT	KT	MT	KT	TT	
G	gorilla		KT	KT	MT	KT	TT	
P	abelii		KT	KT	MT	KT	TT	
H	moloch		KT	KT	MT	KT	TT	
N	leucogenys		KT	KT	MT	KT	TT	
P	anubis		KT	KT	MT	KT	TT	
M	leucophaeu		KT	KT	MT	KT	TT	
C	atys		KT	KT	MT	KT	TT	
M	nemestrina		KT	KT	MT	KT	TT	
M	mulatta		KT	KT	MT	KT	TT	
M	fascicularis		KT	KT	MT	KT	TT	
C	sabaeus		KT	KT	MT	KT	TT	
T	gelada		KT	KT	MT	KT	TT	
P	tephroscele		KT	KT	MT	KT	TT	
R	bieti		KT	KT	MT	KT	TT	
R	roxellana		KT	KT	MT	KT	TT	
C	capucinus		KT	KT	MT	KT	TT	
S	boliviensis		KT	KT	MT	KT	TT	
S	apella		KT	KT	MT	KT	TT	
C	jacchus		KT	KT	MT	KT	TT	
A	nancymaae		KT	KT	MT	KT	TT	
P	coquereli		KT	KT	KT	KT	TT	
M	murinus		KT	KT	KT	KT	TT	
O	garnettii		KT	KT	KT	KT	TT	
T	chinensis		KT	KT	MT	KT	TT	
D	ordii		KT	KT	MT	KT	TT	
J	jaculus		KT	KT	MT	KT	TT	
M	flaviventris		KT	KT	MT	KT	TT	
M	marmota		KT	KT	MT	KT	TT	
I	tridecemlin		KT	KT	MT	KT	TT	
C	lanigera		KT	KT	MT	KT	TT	
O	degus		KT	KT	MT	KT	TT	

Genus	species	protein	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a
		residue	12	35 10	55 5	35 58	35 59	35
		Z-score						
N	galili		KT	KT	MT	KT	TT	
H	glaber		KT	KT	MT	KT	TT	
M	ochrogaster		KT	KT	MT	KT	TT	
C	griseus		KT	KT	MT	KT	TT	
P	maniculatus		KT	KT	MT	KT	TT	
M	auratus		KT	KT	MT	KT	TT	
R	norvergicus		KT	KT	MT	KT	TT	
M	pahari		KT	KT	MT	KT	TT	
M	caroli		KT	KT	MT	KT	TT	
M	musculus		KT	KT	MT	KT	TT	
O	princeps		KT	KT	MT	KT	TT	
O	cuniculus		KT	KT	MT	KT	TT	
S	scrofa		KT	KT	MT	KT	TT	
C	hircus		KT	KT	MT	KT	TT	
O	aries		KT	KT	MT	KT	TT	
O	virginianus		KT	KT	MT	KT	TT	
B	taurus		KT	KT	MT	KT	TT	
B	mutus		KT	KT	MT	KT	TT	
B	bubalis		KT	KT	MT	KT	TT	
C	ferus		KT	KT	MT	KT	TT	
B	acutorostrat		KT	KT	MT	KT	TT	
L	obliquidens		KT	KT	MT	KT	TT	
G	melas		KT	KT	MT	KT	TT	
O	orca		KT	KT	MT	KT	TT	
P	sinus		KT	KT	MT	KT	TT	
N	asiaeorienta		KT	KT	MT	KT	TT	
D	leucas		KT	KT	MT	KT	TT	
M	monoceros		KT	KT	MT	KT	TT	
L	vexillifer		KT	KT	MT	KT	TT	
C	simum		KT	KT	KT	KT	TT	
E	asinus		KT	KT	MT	KT	TT	
E	caballus		KT	KT	MT	KT	TT	
F	catus		KT	KT	MT	KT	TT	
A	jubatus		KT	KT	MT	KT	TT	

Genus	species	protein	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a
		residue	12	35 10	55 5	35 58	35 59	35
		Z-score						
P	vitulina		KT	KT	MT	KT	TT	
L	weddellii		KT	KT	MT	KT	TT	
N	schauinslan		KT	KT	MT	KT	TT	
Z	californianu		KT	KT	MT	KT	TT	
U	arctos		KT	KT	MT	KT	TT	
M	putorius		KT	KT	MT	KT	TT	
M	erminea		KT	KT	MT	KT	TT	
C	lupus		KT	KT	MT	KT	TT	
P	discolor		KT	KT	MT	KT	TT	
M	natalensis		KT	RT	MT	KT	TT	
E	fuscus		KT	KT	MT	KT	TT	
M	brandtii		KT	KT	MT	KT	TT	
M	lucifugus		KT	KT	MT	KT	TT	
R	aegyptiacus		KT	KT	MT	KT	TT	
C	cristata		KT	KT	MT	KT	TT	
E	europaeus		KA	KT	MA	KA	TA	
E	edwardii		KT	KT	MT	KT	TT	
D	novemcinct		KT	KT	MT	KT	TT	
A	sinensis		KT	KT	MT	KT	TT	
A	mississippie		KT	KT	MT	KT	TT	
P	muralis		KT	RS	MT	KT	TT	
A	carolinensis		KT	KS	MT	KT	TT	
P	vitticeps		KT	KS	MT	KT	TT	
P	bivittatus		KT	KS	MT	KT	TT	
T	carolina		KT	KS	MT	KT	TT	
C	picta		KT	KS	MT	KT	TT	
G	evgoodei		KT	KS	MT	KT	TT	
X	tropicalis		KT	KS	MT	KT	TT	
X	laevis		KS	KS	MS	KS	TS	
R	bivittatum		KT	KS	MT	KT	TT	
A	mexicanum		KT	KS	MT	KT	TT	
L	chalumnae		KS	KS	MS	KS	TS	
E	calabaricus		KT	KT	MT	KT	TT	
P	kingsleyae		KT	KT	MT	KT	TT	

Genus	species	protein	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a	αS 4a
		residue	12	35 10	55 5	35 58	35 59	35
		Z-score						
S	formosus		KT	KT	MT	KT	TT	
A	mexicanus		KA	KT	KA	KA	TA	
P	nattereri		KT	KT	KT	KT	TT	
D	clupeoides		KT	KT	MT	KT	TT	
E	electricus		KT	KT	MT	KT	TT	
S	salar		KT	KS	MT	KT	TT	
S	trutta		KT	KS	MT	KT	TT	
O	mykiss		KT	KS	MT	KT	TT	
O	kisutch		KT	KS	MT	KT	TT	
G	morhua		KA	RS	LA	KA	TA	
P	formosa		KT	KT	MT	KT	TT	
P	reticulata		KT	KT	MT	KT	TT	
P	latipinna		KT	RS	MT	KT	TT	
P	mexicana		KT	KT	MT	KT	TT	
X	hellerii		KT	KS	MT	KT	TT	
X	couchianus		KT	KS	MT	KT	TT	
X	maculatus		KT	KS	MT	KT	TT	
C	variegatus		KT	KT	MT	KT	TT	
T	rubripes		KS	KS	MS	KS	TS	
M	armatus		KT	KT	MT	KT	TT	
O	latipes		KT	KT	MT	KT	TT	
A	testudineus		KT	KT	MT	KT	TT	
B	splendens		KT	KS	MT	KT	TT	
O	niloticus		KT	KT	MT	KT	TT	
H	burtoni		KT	KT	MT	KT	TT	
M	zebra		KT	KT	MT	KT	TT	
N	brichardi		KT	KT	MT	KT	TT	
L	bergylta		KS	RS	MS	KS	TS	
A	ocellatus		RA	KS	KA	-A	AA	
C	gobio		KS	KT	LS	-S	AS	
S	lucioperca		RA	KT	MA	-A	AA	
L	crocea		KT	KT	IT	KT	TT	
S	aurata		KT	KT	MT	KT	TT	
C	milii		KT	KS	MT	KT	TT	

Supp. Fig. 4G

β-syn. αIa-tub.			Correlated pairs				
		protein	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a
Genus	species	residue	38 440	16 440	49 440	13 440	45 440
		Z-score	10.8	10.8	10.7	10.5	10.5
H	sapiens		LV	VV	VV	VV	RV
P	troglodytes		LV	VV	VV	VV	RV
G	gorilla		LV	VV	VV	VV	RV
P	abelii		LV	VV	VV	VV	RV
H	moloch		LV	VV	VV	VV	RV
N	leucogenys		LV	VV	VV	VV	RV
M	leucophaeu		LV	VV	VV	VV	RV
M	nemestrina		LV	VV	VV	VV	RV
M	mulatta		LV	VV	VV	VV	RV
M	fascicularis		LV	VV	VV	VV	RV
C	sabaeus		LV	VV	VV	VV	RV
P	tephroscele		LV	VV	VV	VV	RV
R	roxellana		LV	VV	VV	VV	RV
C	capucinus		LV	VV	VV	VV	RV
S	boliviensis		LV	VV	VV	VV	RV
S	apella		LV	VV	VV	VV	RV
C	jacchus		LV	VV	VV	VV	RV
A	nancymaae		LV	VV	VV	VV	RV
P	coquereli		LV	VV	VV	VV	RV
M	murinus		LV	VV	VV	VV	RV
O	garnettii		LV	VV	VV	VV	RV
D	ordii		LV	VV	VV	VV	RV
M	flaviventris		LV	VV	VV	VV	RV
M	marmota		LV	VV	VV	VV	RV
I	tridecemlin		LV	VV	VV	VV	RV
C	porcellus		LV	VV	VV	VV	RV
C	griseus		LV	VV	VV	VV	KV
P	leucopus		LV	VV	VV	VV	KV
R	norvegicus		LV	VV	VV	VV	KV
M	musculus		LV	VV	VV	VV	SV
O	cuniculus		LV	VV	VV	VV	RV
S	scrofa		LV	VV	VV	VV	RV
C	hircus		LV	VV	VV	VV	RV
O	aries		LV	VV	VV	VV	RV

		protein	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a
Genus	species	residue	38 440	16 440	49 440	13 440	45 440
O	virginianus		LV	VV	VV	VV	RV
B	taurus		LV	VV	VV	VV	RV
B	mutus		LV	VV	VV	VV	RV
B	bubalis		LV	VV	VV	VV	RV
B	bison		LV	VV	VV	VV	RV
C	ferus		LV	VV	VV	VV	RV
L	obliquidens		LV	VV	VV	VV	RV
G	melas		LV	VV	VV	VV	RV
O	orca		LV	VV	VV	VV	RV
P	sinus		LV	VV	VV	VV	RV
D	leucas		LV	VV	VV	VV	RV
M	monoceros		LV	VV	VV	VV	RV
L	vexillifer		LV	VV	VV	VV	RV
C	simum		LV	VV	VV	VV	RV
E	asinus		LV	VV	VV	VV	RV
E	caballus		LV	VV	VV	VV	RV
P	pardus		LV	VV	VV	VV	RV
L	canadensis		LV	VV	VV	VV	RV
F	catus		LV	VV	VV	VV	RV
A	jubatus		LV	VV	VV	VV	RV
P	vitulina		LV	VV	VV	VV	RV
N	schainslandi		LV	VV	VV	VV	RV
U	arctos		LV	VV	VV	VV	RV
M	putorius		LV	VV	VV	VV	RV
M	erminea		LV	VV	VV	VV	RV
C	lupus		LV	VV	VV	VV	RV
P	discolor		LV	VV	VV	VV	RV
E	fuscus		LV	VV	VV	VV	RV
M	brandtii		LV	VV	VV	VV	RV
M	lucifugus		LV	VV	VV	VV	RV
R	aegyptiacus		LV	VV	VV	VV	RV
O	afer		LV	VV	VV	VV	RV
C	asiatica		LV	VV	VV	VV	RV
D	novemcinct		LV	VV	VV	VV	RV

		protein	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a
Genus	species	residue	38 440	16 440	49 440	13 440	45 440
S	harrisi		LV	VV	VV	VV	RV
P	cinereus		LV	VV	VV	VV	RV
O	anatinus		LV	VV	VV	VV	RV
C	coturnix		LV	VV	VV	VV	-V
G	gallus		LV	VV	VV	VV	-V
C	anna		LV	VV	VV	VV	-V
P	filicauda		LV	VV	VV	VV	-V
C	altera		LV	VV	VV	VV	-V
C	moneduloid		LV	VV	VV	VV	-V
T	guttata		LV	VV	VV	VV	-V
P	humilis		LV	VV	VV	VV	-V
P	muralis		LV	VV	AV	VV	RV
A	carolinensis		LV	AV	AV	VV	RV
P	vitticeps		LV	VV	AV	VV	RV
P	bivittatus		LI	VI	VI	VI	RI
T	elegans		LV	VV	VV	VV	RV
P	mucrosqua		LV	VV	VV	VV	RV
G	evgoodei		LV	VV	VV	VV	-V
X	tropicalis		LV	VV	VV	VV	RV
X	laevis		LV	VV	VV	VV	RV
N	parkeri		MV	VV	VV	VV	RV
R	bivittatum		LV	VV	VV	VV	RV
A	mexicanum		LV	VV	VV	VV	RV
M	unicolor		LV	VV	VV	VV	RV
G	seraphini		LV	VV	VV	VV	RV
L	chalumnae		LV	VV	-V	VV	KV
E	calabaricus		LV	AV	VV	MV	KV
L	oculatus		MI	AI	VI	MI	KI
P	kingsleyae		MI	AI	-I	MI	KI
S	formosus		MV	AV	-V	MV	KV
A	mexicanus		MI	AI	-I	MI	KI
C	carpio		MI	AI	-I	MI	KI
P	nattereri		MI	AI	-I	MI	KI
D	clupeoides		MV	AV	-V	MV	KV

		protein	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a	βS 1a
Genus	species	residue	38	480	16	480	49	480	15	480	45	480
D	rerio		MV	AV	-V	MV	KV
S	anshuiensis		MI	AI	-I	MI	KI
S	rhinoceros		MI	AI	-I	MI	KI
E	electricus		MI	AI	-I	MI	KI
I	punctatus		MI	AI	-I	MI	KI
T	fulvidraco		MI	AI	-I	MI	KI
S	salar		MI	AI	-I	MI	KI
S	trutta		MI	AI	-I	MI	KI
O	mykiss		MI	AI	-I	MI	KI
O	kisutch		MI	AI	-I	MI	KI
F	formosa		MI	AI	-I	MI	KI
P	latipinna		MI	AI	-I	MI	KI
P	mexicana		MI	AI	-I	MI	KI
X	hellerii		MI	AI	-I	MI	KI
X	couchianus		MV	AV	-V	MV	KV
X	maculatus		MI	AI	-I	MI	KI
M	armatus		MI	AI	-I	MI	KI
F	heteroclitus		MI	AI	-I	MI	KI
O	latipes		MI	AI	-I	MI	KI
A	testudineus		MI	AI	-I	MI	KI
B	splendens		MI	AI	-I	MI	KI
O	niloticus		MI	AI	-I	MI	KI
H	burtoni		MI	AI	-I	MI	KI
M	zebra		MI	AI	-I	MI	KI
N	brichardi		MI	AI	-I	MI	KI
L	bergylta		MV	AV	-V	MV	KV
C	gobio		MI	AI	-I	MI	KI
S	lucioperca		MI	AI	-I	MI	KI
L	crocea		MV	AV	-V	MV	KV
S	aurata		MV	AV	-V	MV	KV
C	milii		MI	VI	-I	VI	KI
A	radiata		LI	AI	-I	VI	KI

Supp. Fig. 4H

β-syn. βI-tub.			Correlated pairs					
		protein	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81
Genus	species	residue	4 437	125 437	437 13	200 132	55 26	64
		Z-score	8.1	7.0	6.9	6.7	6.6	
H	sapiens		FG	EG	EY	PT	VI	
P	troglodytes		FG	EG	EY	PT	VI	
G	gorilla		FG	EG	EY	PT	VI	
P	abelii		FG	EG	EY	PT	VI	
H	moloch		FG	EG	EY	PT	VI	
N	leucogenys		FG	EG	EY	PT	VI	
P	anubis		FG	EG	EY	PT	VI	
M	leucophaeu		FG	EG	EY	PT	VI	
C	atys		FG	EG	EY	PT	VI	
M	nemestrina		FG	EG	EY	PT	VI	
M	mulatta		FG	EG	EY	PT	VI	
M	fascicularis		FG	EG	EY	PT	VI	
C	sabaeus		FG	EG	EY	PT	VI	
T	gelada		FG	EG	EY	PT	VI	
P	tephroscele		FG	EG	EY	PT	VI	
R	bieti		FG	EG	EY	PT	VI	
R	roxellana		FG	EG	EY	PT	VI	
S	boliviensis		FG	EG	EY	PT	VI	
S	apella		FG	EG	EY	PT	VI	
A	nancymaae		FG	EG	EY	PT	VI	
P	coquereli		FG	EG	EY	PT	VI	
M	murinus		FG	EG	EY	PT	VI	
T	chinensis		FG	EG	EY	PT	VI	
D	ordii		FG	EG	EY	PT	VI	
J	jaculus		FG	EG	EY	PT	VI	
M	flaviventris		FG	EG	EY	PT	VI	
M	marmota		FG	EG	EY	PT	VI	
I	tridecemli		FG	EG	EY	PT	VI	
F	damarensis		FG	EG	EY	PT	VI	
C	lanigera		FG	EG	EY	PT	VI	
C	porcellus		FG	EG	EY	PT	VI	
H	glaber		FG	EG	EY	PT	VI	
M	ochrogaster		FG	EG	EY	PT	VI	
C	griseus		FG	EG	EY	PT	VI	
M	ungiculatu		FG	EG	EY	PT	VI	
P	maniculatus		FG	EG	EY	PT	VI	
P	leucopus		FG	EG	EY	PT	VI	
M	auratus		FG	EG	EY	PT	VI	
R	norvegicus		FG	EG	EY	PT	VI	
M	pahari		FG	EG	EY	PT	VI	
M	caroli		FG	EG	EY	PT	VI	
M	musculus		FG	EG	EY	PT	VI	

		protein	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81
Genus	species	residue	4	437 125	437 13	200 132	55 26	64
O	princeps		FG	EG	EY	PT	VI	
O	cuniculus		FG	EG	EY	PT	VI	
S	scrofa		FG	EG	EY	PT	VI	
C	hircus		FG	EG	EY	PT	VI	
O	aries		FG	EG	EY	PT	VI	
O	virginianus		FG	EG	EY	PT	VI	
B	taurus		FG	EG	EY	PT	VI	
B	mutus		FG	EG	EY	PT	VI	
B	bubalis		FG	EG	EY	PT	VI	
C	ferus		FG	EG	EY	PT	VI	
C	dromedariu		FG	EG	EY	PT	VI	
V	pacos		FG	EG	EY	PT	VI	
B	acutorostrat		FG	EG	EY	PT	VI	
L	obliquidens		FG	EG	EY	PT	VI	
G	melas		FG	EG	EY	PT	VI	
O	orca		FG	EG	EY	PT	VI	
P	sinus		FG	EG	EY	PT	VI	
N	asiaeorienta		FG	EG	EY	PT	VI	
D	leucas		FG	EG	EY	PT	VI	
M	monoceros		FG	EG	EY	PT	VI	
L	vexillifer		FG	EG	EY	PT	VI	
C	simum		FG	EG	EY	PT	VI	
E	asinus		FG	EG	EY	PT	VI	
E	caballus		FG	EG	EY	PT	VI	
P	pardus		FG	EG	EY	PT	VI	
L	canadensis		FG	EG	EY	PT	VI	
L	pardinus		FG	EG	EY	PT	VI	
F	catus		FG	EG	EY	PT	VI	
A	jubatus		FG	EG	EY	PT	VI	
P	vitulina		FG	EG	EY	PT	VI	
N	schainslandi		FG	EG	EY	PT	VI	
O	rosmarus		FG	EG	EY	PT	VI	
U	arctos		FG	EG	EY	PT	VI	
M	putorius		FG	EG	EY	PT	VI	
M	erminea		FG	EG	EY	PT	VI	
C	lupus		FG	EG	EY	PT	VI	
V	vulpes		FG	EG	EY	PT	VI	
M	javanica		FG	EG	EY	PT	VI	
P	discolor		FG	EG	EY	PT	VI	
E	fuscus		FG	EG	EY	PT	VI	
M	brandtii		FG	EG	EY	PT	VI	
R	aegyptiacus		FG	EG	EY	PT	VI	

		protein	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81
Genus	species	residue	4	437 125	437 13	200 132	55 26	28	64
P	alecto		FG	EG	EY	PT	VI		
C	cristata		FG	EG	EY	PT	VI		
O	afer		FG	EG	EY	PT	VI		
C	asiatica		FG	EG	EY	PT	VI		
E	telfairi		FG	EG	EY	PT	VI		
T	manatus		FG	EG	EY	PT	VI		
D	novemcinct		FG	EG	EY	PT	VI		
S	harrisi		FG	EG	EY	PT	VI		
V	ursinus		FG	EG	EY	PT	VI		
O	anatinus		FG	EG	EY	PT	VI		
N	perdicaria		FG	EG	EY	PT	VI		
P	colchicus		FG	EG	EY	PT	VI		
G	gallus		FG	EG	EY	PT	VI		
A	chrysaetos		FG	EG	EY	PT	VI		
P	fasciata		FG	EG	EY	PT	VI		
M	undulatus		FG	EG	EY	PT	VI		
P	filicauda		FG	EG	EY	PT	VI		
C	moneduloid		FG	EG	EY	PT	VI		
T	guttata		FG	EG	EY	PT	VI		
L	striata		FG	EG	EY	PT	VI		
P	humilis		FG	EG	EY	PT	VI		
P	muralis		FG	EG	EY	PT	VI		
A	carolinensis		FG	EG	EY	PT	VI		
P	vitticeps		FG	EG	EY	PT	VI		
P	bivittatus		FG	EG	EY	PT	VI		
T	elegans		FG	EG	EY	PT	VI		
T	sirtalis		FG	EG	EY	PT	VI		
P	mucrosqua		FG	EG	EY	PT	VI		
T	carolina		FG	-G	EY	PT	VI		
C	picta		FG	-G	EY	PT	VI		
G	evgoodei		FG	-G	EY	PT	VI		
C	mydas		FG	-G	EY	PT	VI		
X	tropicalis		LN	DN	EY	PT	VI		
X	laevis		LN	DN	EY	PT	VI		
R	bivittatum		FG	DG	EY	PT	VI		
M	unicolor		FG	EG	EY	PT	VI		
G	seraphini		LG	EG	EY	PT	VI		
L	chalumnae		LE	GE	EY	PS	VI		
E	calabaricus		LE	DE	EY	PT	VI		
A	ruthenus		FE	EE	EY	PT	VI		
L	oculatus		FE	EE	EY	PT	VI		
P	kingsleyae		LE	EE	EY	PT	VI		

		protein	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81	βS 81
Genus	species	residue	4	437 125	437 13	200 132	55 26	55	64
S	formosus		LE	EE	EY	PT	VI		
A	mexicanus		FE	EE	EY	PT	VI		
C	carpio		FD	DD	EY	PT	VI		
P	nattereri		FE	EE	EY	PT	VI		
D	clupeoides		LE	EE	EY	PT	VI		
P	hypophthal		FE	EE	EY	PT	VI		
D	rerio		FE	EE	EY	PT	VI		
S	rhinoceros		LE	DE	EY	PT	VI		
I	punctatus		FE	-E	EY	PT	VI		
T	fulvidraco		FE	QE	EY	PT	VI		
S	salar		FE	EE	DF	QS	AV		
S	trutta		FE	EE	DF	QS	AV		
O	mykiss		FE	-E	DF	QS	AV		
O	kisutch		FE	EE	DF	QS	AV		
G	morhua		FD	-D	EF	PS	VI		
P	formosa		FE	EE	EY	PT	VI		
P	reticulata		FE	EE	EY	PT	VI		
P	latipinna		FE	EE	EY	PT	VI		
P	mexicana		FE	EE	EY	PT	VI		
X	hellerii		FE	EE	EY	PT	VI		
X	couchianus		FE	EE	EY	PT	VI		
X	maculatus		FE	EE	EY	PT	VI		
C	variegatus		FE	EE	EY	PT	VI		
T	rubripes		FE	EE	EY	PT	VI		
M	armatus		FE	EE	EY	PT	VI		
F	heteroclitus		FE	EE	EY	QS	VI		
O	latipes		FE	EE	EY	PT	VI		
A	testudineus		FE	-E	EY	PT	VI		
B	splendens		FE	-E	EY	PT	VI		
O	niloticus		FE	EE	EY	PT	VI		
H	burtoni		FE	EE	EY	PT	VI		
M	zebra		FE	EE	EY	PT	VI		
N	brichardi		FE	EE	EY	PT	VI		
L	bergylta		FE	EE	EY	PT	VI		
A	ocellatus		FE	GE	EY	PT	VI		
C	gobio		FE	GE	EY	PT	VI		
S	lucioperca		FE	EE	EY	PT	VI		
L	crocea		FE	EE	EY	PT	VI		
S	aurata		FE	EE	EY	PT	VI		
C	milii		FE	EE	DF	PS	VI		
S	toraiame		FE	EE	EF	PS	VV		

Supp. Fig. 4I

β-syn βIIa-tub.			Correlated pairs				
		protein	βS 2a	βS 2a	βS 2a	βS 2a	βS 2a
Genus	species	residue	40	125 231	231 231	71 231	126 231	117 443
		Z-score	12.0	12.0	11.4	10.8	10.6
H	sapiens		VA	EA	FA	EA	ED
P	troglodytes		VA	EA	FA	EA	ED
P	paniscus		VA	EA	FA	EA	ED
G	gorilla		VA	EA	FA	EA	ED
P	abelii		VA	EA	FA	EA	ED
N	leucogenys		VA	EA	FA	EA	ED
P	anubis		VA	EA	FA	EA	ED
M	leucophaeu		VA	EA	FA	EA	ED
C	atys		VA	EA	FA	EA	ED
M	nemestrina		VA	EA	FA	EA	ED
M	mulatta		VA	EA	FA	EA	ED
M	fascicularis		VA	EA	FA	EA	ED
C	sabaeus		VA	EA	FA	EA	ED
T	gelada		VA	EA	FA	EA	ED
R	roxellana		VA	EA	FA	EA	ED
C	capucinus		VA	EA	FA	EA	ED
S	boliviensis		VA	EA	FA	EA	ED
S	apella		VA	EA	FA	EA	ED
C	jacchus		VA	EA	FA	EA	ED
M	murinus		VA	EA	FA	EA	ED
D	ordii		VA	EA	FA	EA	ED
J	jaculus		VA	EA	FA	DA	ED
M	marmota		VA	EA	FA	EA	ED
I	tridecemlin		VA	EA	FA	EA	ED
F	damarensis		VA	EA	FA	EA	ED
C	lanigera		VA	EA	FA	EA	ED
O	degus		VA	EA	FA	EA	ED

			Correlated pairs				
		protein	βS 2a	βS 2a	βS 2a	βS 2a	βS 2a
Genus	species	residue	40	125 231	231 231	71 231	126 231	117 443
C	porcellus		VA	EA	FA	EA	ED
N	galili		VA	EA	FA	EA	ED
H	glaber		VA	EA	FA	EA	ED
M	ochrogaster		VA	EA	FA	EA	ED
C	griseus		VA	EA	FA	EA	ED
P	maniculatus		VA	EA	FA	EA	ED
P	leucopus		VA	EA	FA	EA	ED
M	auratus		VA	EA	FA	EA	ED
R	norvegicus		VA	EA	FA	EA	ED
M	musculus		VA	EA	FA	EA	ED
O	princeps		VA	EA	FA	EA	ED
O	cuniculus		VA	EA	FA	DA	ED
S	scrofa		VA	EA	FA	EA	ED
C	hircus		VA	EA	FA	EA	ED
O	aries		VA	EA	FA	EA	ED
B	taurus		VA	EA	FA	EA	ED
B	bubalis		VA	EA	FA	EA	ED
B	bison		VA	EA	FA	EA	ED
C	ferus		VA	EA	FA	EA	ED
C	dromedariu		VA	EA	FA	EA	ED
B	acutorostrat		VA	EA	FA	EA	ED
L	obliquidens		VA	EA	FA	EA	ED
O	orca		VA	EA	FA	EA	ED
P	sinus		VA	EA	FA	EA	ED
D	leucas		VA	EA	FA	EA	ED
M	monoceros		VA	EA	FA	EA	ED
L	vexillifer		VA	EA	FA	EA	ED

			Correlated pairs				
		protein	βS 2a	βS 2a	βS 2a	βS 2a	βS 2a
Genus	species	residue	40	125 231	231 231	71 231	126 231	117 443
C	simum		VA	EA	FA	EA	ED
E	caballus		VA	EA	FA	EA	ED
P	pardus		VA	EA	FA	EA	ED
L	canadensis		VA	EA	FA	EA	ED
F	catus		VA	EA	FA	EA	ED
A	jubatus		VA	EA	FA	EA	ED
P	vitulina		VA	EA	FA	EA	ED
N	schauinslan		VA	EA	FA	EA	ED
O	rasmarus		VA	EA	FA	EA	ED
Z	californianu		VA	EA	FA	EA	ED
U	arctos		VA	EA	FA	EA	ED
M	putorius		VA	EA	FA	EA	ED
M	erminea		VA	EA	FA	EA	ED
C	lupus		VA	EA	FA	EA	ED
V	vulpes		VA	EA	FA	EA	ED
P	discolor		VA	EA	FA	EA	ED
H	armiger		VA	EA	FA	EA	ED
E	fuscus		VA	EA	FA	EA	ED
M	brandtii		VA	EA	FA	EA	VE
M	lucifugus		VA	EA	FA	EA	VE
R	aegyptiacus		VA	EA	FA	EA	ED
P	alecto		VA	EA	FA	EA	ED
C	cristata		VA	EA	FA	EA	ED
E	europaeus		VA	EA	FA	EA	ED
O	afer		VA	EA	FA	DA	ED
C	asiatica		VA	EA	FA	EA	ED
E	telfairi		VA	EA	FA	EA	EE

			Correlated pairs				
		protein	βS 2a	βS 2a	βS 2a	βS 2a	βS 2a
Genus	species	residue	40	125 231	231 231	71 231	126 231	117 443
T	manatus		VA	EA	FA	EA	EE
D	novemcinct		VA	EA	FA	EA	EE
S	harrisii		VA	EA	FA	EA	EE
V	ursinus		VA	EA	FA	EA	EE
P	cinereus		VA	EA	FA	EA	EE
O	anatinus		VA	EA	FA	EA	EE
N	perdicaria		VA	EA	FA	EA	EE
C	coturnix		VA	EA	FA	EA	EE
G	gallus		VA	EA	FA	EA	EE
A	fuligula		VA	EA	FA	EA	EE
A	chrysaetos		VA	EA	FA	EA	EE
C	anna		VA	EA	FA	EA	EE
M	undulatus		VA	EA	FA	EA	EE
P	filicauda		VA	EA	FA	EA	EE
N	chrysocepha		VA	EA	FA	EA	EE
C	moneduloid		VA	EA	FA	EA	EE
T	guttata		VA	EA	FA	EA	EE
L	striata		VA	EA	FA	EA	EE
P	humilis		VA	EA	FA	EA	EE
P	muralis		VA	EA	FA	EA	EE
A	carolinensis		VA	EA	FA	EA	EE
P	vitticeps		VA	EA	MA	EA	EE
T	elegans		VA	EA	FA	EA	EE
P	mucrosqua		VA	EA	FA	EA	EE
G	evgoodei		MI	-I	II	DI	EE
C	mydas		MI	-I	II	DI	EE

Supp. Fig. 4J

β-syn. βIIb-tub.			Correlated pairs						
		protein	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b
Genus	species	residue	4 59	59 2	2 441	441 115	115 223	223 -2	-2 440	95 443
		Z-score	9.6	8.9	8.7	7.5	7.4
H	sapiens		FY	DG	EG	DE	PG
P	troglodytes		FY	DG	EG	DE	PG
P	paniscus		FY	DG	EG	DE	PG
G	gorilla		FY	DG	EG	DE	PG
P	abelii		FY	DG	EG	DE	PG
N	leucogenys		FY	DG	EG	DE	PG
P	anubis		FY	DG	EG	DE	PG
M	leucophaeu		FY	DG	EG	DE	PG
C	atys		FY	DG	EG	DE	PG
M	nemestrina		FY	DG	EG	DE	PG
M	mulatta		FY	DG	EG	DE	PG
M	fascicularis		FY	DG	EG	DE	PG
C	sabaeus		FY	DG	EG	DE	PG
T	gelada		FY	DG	EG	DE	PG
P	tephroscele		FY	DG	EG	DE	PG
R	roxellana		FY	DG	EG	DE	PG
C	capucinus		FY	DG	EG	DE	PG
S	boliviensis		FY	DG	EG	DE	PG
S	apella		FY	DG	EG	DE	PG
A	nancymaae		FY	DG	EG	DE	PG
M	murinus		FY	DG	EG	DE	PG
O	garnettii		FY	DG	EG	DE	PG
T	chinensis		FY	DG	EG	DE	PG
D	ordii		FY	DG	EG	DE	PG
J	jaculus		FY	DG	EG	DE	PG
M	flaviventris		FY	DG	EG	DE	PG
M	marmota		FY	DG	EG	DE	PG
I	tridecemlin		FY	DG	EG	DE	PG
F	damarensis		FY	DG	EG	DE	PG
C	lanigera		FY	DG	EG	DE	PG
C	porcellus		FY	DG	EG	DE	PG
N	galili		FY	DG	EG	DE	PG
H	glaber		FY	DG	EG	DE	PG
M	ochrogaster		FY	DG	EG	DE	PG
C	griseus		FY	DG	EG	DE	PG
M	unguiculatu		FY	DG	EG	DE	AG

			Correlated pairs						
		protein	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b
Genus	species	residue	4 59	59 2	2 441	441 115	115 223	223 -2	-2 440	95 443
P	maniculatus		FY	DG	EG	DE	PG
P	leucopus		FY	DG	EG	DE	PG
R	norvegicus		FY	DG	EG	DE	PG
M	caroli		FY	DG	EG	DE	PG
M	musculus		FY	DG	EG	DE	PG
O	princeps		FY	DG	EG	DE	PG
O	cuniculus		FY	DG	EG	DE	PG
S	scrofa		FY	DG	-G	DE	PG
C	hircus		FY	DG	EG	DE	PG
O	aries		FY	DG	EG	DE	PG
O	virginianus		FY	DG	EG	DE	PG
B	taurus		FY	DG	EG	DE	PG
B	mutus		FY	DG	EG	DE	PG
B	bubalis		FY	DG	EG	DE	PG
C	ferus		FY	DG	EG	DE	PG
C	dromedariu		FY	DG	EG	DE	PG
B	acutorostrat		FY	DG	EG	DE	PG
L	obliquidens		FY	DG	EG	DE	PG
G	melas		FY	DG	EG	DE	PG
O	orca		FY	DG	EG	DE	PG
P	sinus		FY	DG	EG	DE	PG
N	asiaeorienta		FY	DG	EG	DE	PG
D	leucas		FY	DG	EG	DE	PG
M	monoceros		FY	DG	EG	DE	PG
L	vexillifer		FY	DG	EG	DE	PG
C	simum		FY	DG	EG	DE	PG
E	asinus		FY	DG	EG	DE	PG
E	caballus		FY	DG	EG	DE	PG
P	pardus		FY	DG	EG	DE	PG
L	canadensis		FY	DG	EG	DE	PG
L	pardinus		FY	DG	EG	DE	PG
F	catus		FY	DG	EG	DE	PG
A	jubatus		FY	DG	EG	DE	PG
P	vitulina		FY	DG	EG	DE	PG
N	schainslandi		FY	DG	EG	DE	PG
O	rosmarus		FY	DG	EG	DE	PG

			Correlated pairs						
		protein	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b
Genus	species	residue	4 59	59 2	2 441	441 115	115 223	223 -2	-2 440	95 443
U	arctos		FY	DG	EG	DE	PG
A	melanoleuc		FY	DG	EG	DE	PG
M	erminea		FY	DG	EG	DE	PG
C	lupus		FY	DG	EG	DE	PG
P	discolor		FY	DG	EG	DE	PG
H	armiger		FY	DG	EG	DE	PG
M	natalensis		FY	DG	EG	DE	PG
E	fuscus		FY	DV	EG	DE	PV
M	lucifugus		FY	DG	E-	DE	PG
R	aegyptiacus		FY	DG	EG	DE	PG
P	alecto		FY	DG	EG	DE	PG
E	europaeus		FY	DG	EG	DE	PG
O	afer		FY	DG	EG	DE	PG
C	asiatica		FY	DG	EG	DE	PG
E	telfairi		FY	DG	EG	DE	PG
E	edwardii		FY	DG	EG	DE	PG
T	manatus		FY	DG	EG	DE	PG
S	harrisii		FY	DG	EG	DE	PG
V	ursinus		FY	DG	EG	DE	PG
P	cinereus		FY	DG	EG	DE	PG
O	anatinus		FY	DG	EG	DE	PG
P	colchicus		FY	EE	EG	EG	AE
G	gallus		FY	EE	EG	EG	AE
A	fuligula		FY	EE	EG	EG	PE
A	chrysaetos		FY	EE	EG	EG	PE
C	anna		FY	EE	EG	EG	PE
E	traillii		FY	EE	EG	EG	AE
P	filicauda		FY	EE	EG	EG	AE
N	chrysocepha		FY	EE	EG	EG	AE
C	moneduloid		FY	EE	EG	EG	AE
T	guttata		FY	EE	EG	EG	AE
L	striata		FY	EE	EG	EG	AE
P	humilis		FY	EE	EG	EG	AE
P	muralis		FY	DE	EG	DG	PE
P	vitticeps		FY	DE	EG	DG	PE
P	bivittatus		FY	DE	EG	DG	PE

			Correlated pairs						
		protein	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b	βS 2b
Genus	species	residue	4 59	59 2	2 441	441 115	115 223	223 -2	-2 440	95 443
T	elegans		FY	DE	EG	DG	PE
P	mucrosqua		FY	DE	DG	DG	PE
C	picta		FY	DE	EG	DG	PE
G	evgoodei		FY	DE	EG	DG	PE
X	tropicalis		LF	DG	EG	DE	PG
X	laevis		LY	DG	EG	DE	PG
N	parkeri		FY	DG	EG	DE	PG
R	bivittatum		FF	DG	EG	DE	PG
A	mexicanum		FY	DG	EG	DE	PG
M	unicolor		FF	EG	EG	EE	PG
G	seraphini		LF	DG	EG	DE	PG
L	chalumnae		LF	DG	EG	DE	PG
L	oculatus		FY	DG	EG	DE	PG
A	mexicanus		FY	DG	EG	D-	PG
P	nattereri		FY	DG	EG	D-	PG
P	hypophthal		FY	DG	EG	D-	TG
D	rerio		FY	DG	EG	D-	PG
S	anshuiensis		LY	DG	EG	D-	PG
S	rhinoceros		LY	DG	EG	D-	PG
E	electricus		FY	DG	QS	D-	PG
I	punctatus		FY	DG	EG	D-	TG
T	fulvidraco		FY	DG	EG	D-	PG
S	salar		FY	DG	EG	D-	PG
S	trutta		FY	DG	EG	D-	PG
O	mykiss		FY	DG	EG	D-	PG
O	kisutch		FY	DG	EG	D-	PG
G	morhua		FY	DG	EG	D-	PG
P	reticulata		FY	DG	EG	D-	PG
P	latipinna		FY	DG	EG	D-	PG
X	hellerii		FY	DG	EG	D-	PG
X	couchianus		FY	DG	EG	D-	PG
X	maculatus		FY	DG	EG	D-	PG
B	splendens		FY	DG	EG	D-	PG
C	milii		FY	DG	EG	DE	PG

Supp. Fig. 4K

Supp. Fig. 4L

Supp. Fig. 4M

γ-syn. βI-tub.

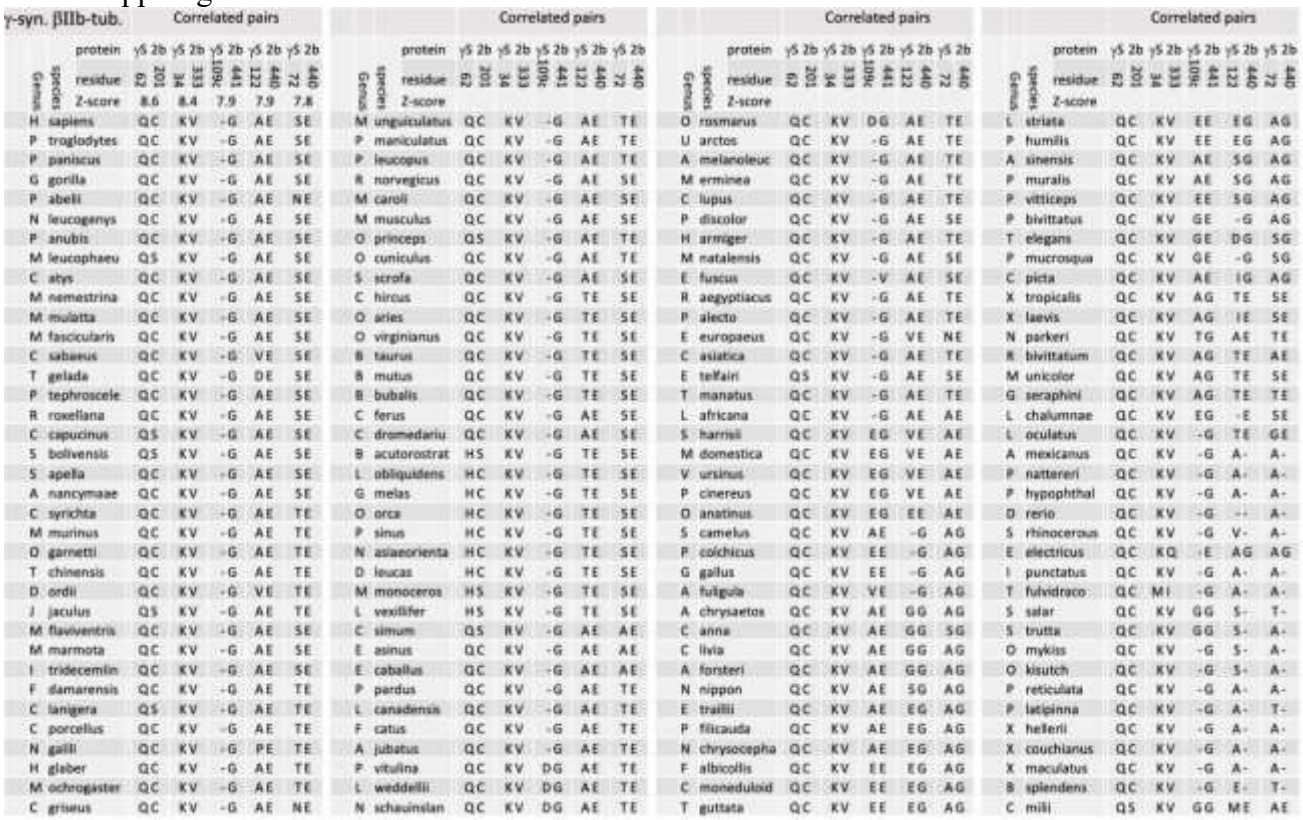
Genus	species	protein	γ5 442	B1 81	γ5 442	B1 58	γ5 64	B1 58	γ5 267	B1 46	γ5 64
		residue	26	81	442	58	64	58	267	46	64
		Z-score	8.0	7.4	6.6	6.6	6.6				
H	sapiens		VE	TE	KI	KM	EI				
P	troglodytes		VE	TE	KI	KM	EI				
G	gorilla		VE	TE	KI	KM	EI				
P	abelii		VE	TE	KI	KM	EI				
H	moloch		VE	TE	KI	KM	EI				
N	leucogenys		VE	TE	KI	KM	EI				
P	anubis		VE	TE	KI	KM	EI				
M	leucophaeu		VE	TE	KI	KM	EI				
C	atys		VE	TE	KI	KM	EI				
M	nemestrina		VE	TE	KI	KM	EI				
M	mulatta		VE	TE	KI	KM	EI				
M	fascicularis		VE	TE	KI	KM	EI				
C	sabaeus		VE	TE	KI	KM	EI				
T	gelada		VE	TE	KI	KM	EI				
P	tephroscele		VE	TE	KI	KM	EI				
R	bieti		VE	TE	KI	KM	EI				
R	roxellana		VE	TE	KI	KM	EI				
S	bolivensis		VE	TE	KI	KM	EI				
S	apella		VE	TE	KI	KM	EI				
A	nancymaae		VE	TE	KI	KM	EI				
C	syrichta		VE	TE	KI	KM	EI				
P	coquereli		VE	TE	KI	KM	EI				
M	murinus		VE	TE	KI	KM	EI				
T	chinensis		VE	TE	KI	KM	EI				
D	ordii		VE	TE	KI	KM	EI				
J	jaculus		VE	TE	KI	KM	EI				
M	flaviventris		VE	TE	KI	KM	EI				
M	marmota		VE	TE	KI	KM	EI				
I	tridecemlin		VE	TE	KI	KM	EI				
F	damarensis		VE	TE	KI	KM	EI				
C	lanigera		VE	TE	KI	KM	EI				
C	porcellus		VE	TE	KI	KM	EI				
H	glaber		VE	TE	KI	KM	EI				
M	ochrogaster		VE	TE	KI	KM	EI				
C	griseus		VE	TE	KI	KM	EI				
M	unguiculatu		VE	TE	KI	KM	EI				
P	maniculatus		VE	TE	KI	KM	EI				
P	leucopus		VE	TE	KI	KM	EI				
M	auratus		VE	TE	KI	KM	EI				
R	norvegicus		VE	TE	KI	KM	GI				
M	pahari		VE	TE	KI	KM	EI				
M	caroli		VE	TE	KI	KM	EI				
M	musculus		VE	TE	KI	KM	EI				
O	princeps		VE	TE	KI	KM	EI				
O	cuniculus		VE	TE	KI	KM	EI				
S	scrofa		VE	TE	KI	KM	EI				
C	hircus		VE	TE	KI	KM	EI				
O	aries		VE	TE	KI	KM	EI				
O	virginianus		VE	TE	KI	KM	EI				
B	taurus		VE	TE	KI	KM	EI				
B	mutus		VE	TE	KI	KM	EI				
B	bubalis		VE	TE	KI	KM	EI				
C	ferus		VE	TE	KI	KM	EI				
C	dromedariu		VE	TE	KI	KM	EI				
V	pacos		VE	TE	KI	KM	EI				
B	acutorostrat		VE	TE	KI	KM	EI				
L	obliquidens		VE	TE	KI	KM	EI				
G	melas		VE	TE	KI	KM	EI				
O	orca		VE	TE	KI	KM	EI				
P	sinus		VE	TE	KI	KM	EI				
N	asiaeorienta		VE	TE	KI	KM	EI				
D	leucas		VE	TE	KI	KM	EI				
M	monoceros		VE	TE	KI	KM	EI				
L	vexillifer		VE	TE	KI	KM	EI				
C	simum		VE	TE	KI	KM	EI				
E	asinus		VE	AE	KI	KM	EI				
E	caballus		VE	AE	KI	KM	EI				
P	pardus		VE	TE	KI	KM	EI				
P	concolor		VE	TE	KI	KM	EI				
L	canadensis		VE	TE	KI	KM	EI				
F	catus		VE	TE	KI	KM	EI				
A	jubatus		VE	TE	KI	KM	EI				
P	vitulina		VE	TE	KI	KM	EI				
L	weddellii		VE	TE	KI	KM	EI				
N	schauinslan		VE	TE	KI	KM	EI				
O	rosmarus		VE	TE	KI	KM	EI				
U	arctos		VE	TE	KI	KM	EI				
M	putorius		VE	TE	KI	KM	EI				
M	erminea		VE	TE	KI	KM	EI				
C	lupus		VE	TE	KI	KM	EI				
V	vulpes		VE	TE	KI	KM	EI				
M	javanica		VE	TE	KI	KM	EI				
P	discolor		VE	TE	KI	KM	EI				
E	fuscus		VE	TE	KI	KM	EI				
	brandtii		VE	TE	KI	KM	EI				
	aegypticus		VE	TE	KI	KM	EI				
	alecto		VE	TE	KI	KM	EI				
	cristata		VE	TE	KI	KM	EI				
	asiatica		VE	TE	KI	KM	EI				
	telfairi		VE	TE	KI	KM	EI				
	manatus		VE	TE	KI	KM	EI				
	novemcinct		VE	TE	KI	KM	EI				
	harrisii		VE	TE	KI	KM	EI				
	domestica		VE	TE	KI	KM	EI				
	ursinus		VE	TE	KI	KM	EI				
	anatinus		VE	TE	KI	KM	EI				
	perdicaria		VE	TE	KI	KM	EI				
	colchicus		VE	TE	KI	KM	EI				
	gallus		VE	TE	KI	KM	EI				
	cunicularia		VE	TE	KI	KM	EI				
	chrysaetos		VE	TE	KI	KM	EI				
	pelagica		VE	TE	KI	KM	EI				
	canorus		VE	TE	KI	KM	EI				
	undulatus		VE	TE	KI	KM	EI				
	filicauda		VE	TE	KI	KM	EI				
	moneduloid		VE	TE	KI	KM	EI				
	caeruleus		VE	TE	KI	KM	EI				
	guttata		VE	TE	KI	KM	EI				
	striata		VE	TE	KI	KM	EI				
	humilis		VE	TE	KI	KM	EI				
	muralis		VE	TE	KI	KM	EI				
	carolinensis		VE	TE	KI	KM	EI				
	vitticeps		VE	TE	KI	KM	EI				
	bivittatus		VE	TE	KI	KM	EI				
	elegans		VE	TE	KI	KM	EI				
	muscrosqua		VE	TE	KI	KM	EI				
	carolina		VE	TE	KI	KM	EI				
	picta		VE	TE	KI	KM	EI				
	mydas		VE	TE	KI	KM	EI				
	tropicalis		VE	TE	KI	KM	EI				
	laevis		VE	TE	KI	KM	EI				
	bivittatum		VE	TE	KI	KM	EI				
	unicolor		VE	TE	KI	KM	EI				
	seraphini		VE	TE	KI	KM	EI				
	chalumnae		VE	TE	KI	KM	EI				
	calabaricus		VE	TE	KI	KM	EI				
L	oculatus		VE	TE	KI	KM	EI				
P	kingsleyae		VE	TE	KI	KM	EI				
S	formosus		VE	TE	KI	KM	EI				
A	mexicanus		VE	TE	KI	KM	EI				
P	nattereri		VE	AE	KI	KM	EI				
D	clupeoides		VE	TE	KI	KM	EI				
P	hypophthal		LD	AD	KI	KM	EI				
D	rerio		VD	AD	KI	KM	EI				
S	rhinocerous		VD	AD	KI	KM	EI				
I	punctatus		LD	AD	KI	KM	EI				
T	fulvidraco		VE	AE	KI	KM	EI				
S	salar		VE	TE	RV	RI	DV				
S	trutta		VE	TE	RV	RI	DV				
O	mykiss		VE	TE	RV	RI	DV				
O	kisutch		VE	TE	RV	RI	DV				
S	alpinus		VE	TE	RV	RI	DV				
P	formosa		VE	TE	KI	KM	EI				
P	reticulata		VE	TE	KI	KM	EI				
P	latipinna		VE	TE	KI	KM	EI				
P	mexicana		VE	TE	KI	KM	EI				
X	helleri		VE	TE	KI	KM	EI				
X	couchianus		VE	TE	KI	KM	EI				
X	maculatus		VE	TE	KI	KM	EI				
C	variegatus		VE	TE	KI	KM	EI				
T	rubripes		VD	AD	KI	KM	EI				
M	armatus		VE	TE	KI	KM	EI				
F	heterociitus		VE	TE	KI	KM	EI				
O	latipes		VE	TE	KI	KM	EI				
A	testudineus		VE	TE	KI	KM	EI				
B	splendens		VE	TE	KI	KM	EI				
O	niloticus		VE	TE	KI	KM	EI				
H	burtoni		VE	TE	KI	KM	EI				
M	zebra		VE	TE	KI	KM	EI				
L	bergylta		VD	TD	KI	KM	EI				
S	lucioperca		VD	AD	KI	KM	EI				
L	crocea		VD	TD	KI	KM	EI				
C	milii		VD	TD	KI	KM	EI				
R	typus		VQ	TQ	KI	KM	EI				
S	torazame		VE	TE	KV	KI	EV				

Supp. Fig. 4N

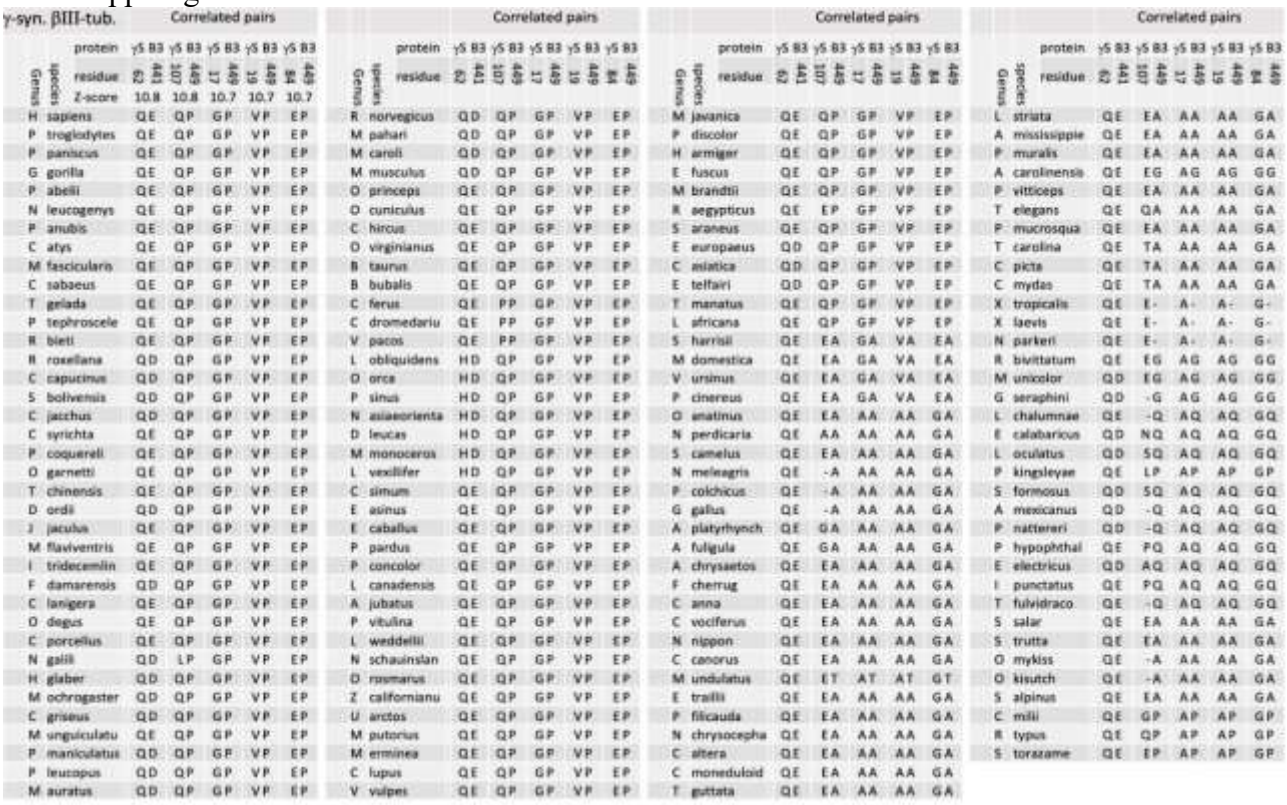
γ-syn. βIIa-tub.

Genus	species	protein	γ5 125	2a 41	γ5 115c	2a 41	γ5 88	2a 55	γ5 115d	2a 41	γ5 100	2a 364
		residue	125	41	115c	41	88	55	115d	41	100	364
		Z-score	10.2	10.0	9.7	9.6	8.8					
H	sapiens		GD	-D	EA	-D	DS					
P	troglodytes		GD	-D	EA	-D	DS					
P	paniscus		GD	-D	EA	-D	DS					
G	gorilla		GD	-D	EA	-D	DS					
P	abelii		GD	-D	EA	-D	DS					
N	leucogenys		RD	-D	EA	-D	DS					
P	anubis		GD	-D	EA	-D	DS					
M	leucophaeu		GD	-D	ET	-D	DS					
C	atys		GD	-D	EA	-D	DS					
M	nemestrina		GD	-D	EA	-D	DS					
M	mulatta		GD	-D	EA	-D	DS					
M	fascicularis		GD	-D	EA	-D	DS					
C	sabaeus		GD	-D	EA	-D	DS					
T	gelada		GD	-D	EA	-D	DS					
R	roxellana		GD	-D	EA	-D	DS					
C	capucinus		GD	-D	DT	-D	DS					
S	bolivensis		GD	-D	DA	-D	DS					
S	apella		GD	-D	DT	-D	DS					
C	jacchus		GD	-D	DT	-D	DS					
C	syrichta		GD	-D	EA	-D	DS					
M	murinus		GD	-D	EA	-D	DS					
D	ordii		GD	-D	EA	-D	DS					
J	jaculus		GD	-D	ET	-D	ES					
M	marmota		GD	-D	EA	-D	DS					
I	tridecemlin		GD	-D	EA	-D	DS					
F	damarensis		ED	-D	EA	-D	DS					
C	lanigera		GD	-D	EA	-D	DS					
O	degus		GD	-D	EA	-D	DS					
C	porcellus		-D	-D	EA	-D	DS					
N	galili		-D	-D	EA	-D	DS					
H	glaber		ED	-D	ET	-D	DS					
M	ochrogaster		GD	-D	EA	-D	DS					
C	griseus		GD	-D	EA	-D	DS					
P	maniculatus		ED	-D	EA	-D	DS					
P	leucopus		ED	-D	EA	-D	DS					
M	auratus		GD	-D	EA	-D	DS					
R	norvegicus		GD	-D	EA	-D	DS					
M	musculus		GD	-D	EA	-D	DS					
O	princeps		VD	-D	EA	-D	DS					
O	cuniculus		GD	-D	EA	-D	DS					
S	scrofa		GD	-D	EA	-D	DS					
C	hircus		GD	-D	EA	-D	AS					
O	aries		GD	-D	EA	-D	AS					
B	taurus		GD	-D	EA	-D	AS					
B	bubalis		GD	-D	EA	-D	AS					
B	bison		GD	-D	DA	-D	AS					
C	ferus		GD	-D	DA	-D	DS					
C	dromedariu		GD	-D	DA	-D	DS					
B	acutorostrat		GD	-D	DA	-D	DS					
L	obliquidens		GD	-D	EA	-D	DS					
O	orca		GD	-D	EA	-D	DS					
P	sinus		GD	-D	EA	-D	DS					
D	leucas		GD	-D	EA	-D	DS					
M	monoceros		GD	-D	EA	-D	DS					
L	vexillifer		GD	-D	EA	-D	DS					
C	simum		GD	-D	EA	-D	DS					
E	caballus		GD	-D	EA	-D	DS					
P	pardus		GD	-D	EA	-D	DS					
L	canadensis		GD	-D	EA	-D	DS					
F	catus		GD	-D	EA	-D	DS					
A	jubatus		GD	-D	EA	-D	DS					
P	vitulina		GD	-D	EA	-D	DS					
L	weddellii		GD	-D	EA	-D	DS					
N	schauinslan		GD	-D	EA	-D	DS					
O	rosmarus		GD	-D	EA	-D	DS					
Z	californianu		GD	-D	EA	-D	DS					
U	arctos		GD	-D	EA	-D	DS					
M	putorius		GD	-D	EA	-D	DS					
M	erminea		GD	-D	EA	-D	DS					
C	lupus		GD	-D	EA	-D	DS					
V	vulpes		GD	-D	EA	-D	DS					
P	discolor		VD	-D	EA	-D	ES					
H	armiger		GD	-D	EA	-D	EA					
E	fuscus		WE	-E	EA	-E	ES					
M	brandtii		WE	-E	DA	-E	ES					
R	aegypticus		GD	-D	EA	-D	ES					
P	alecto		GD	-D	EA	-D	EA					
C	cristata		MD	-D	EA	-D	DS					
E	europaeus		RD	-D	EA	-D	ES					
C	asiatica		GD	-D	ET	-D	DA					
E	telfairi		GD	-D	DT	-D	DS					
T	manatus		GD	-D	EA	-D	DS					
L	africana		GD	-D	EA	-D	DS					
D	novemcinct		ED	-D	DA	-D	SS					
S	harrisii		SD	-D	DA	-D	DS					
M	domestica		SD	-D	DA	-D	DS					
V	ursinus		SD	-D	DA	-D	DS					
P	cinereus		SD	-D	DA	-D	DS					
O	anatinus		GD	ED	EA	VD	DS					
N	perdicaria		GD	-D	EA	-D	ES					
T	guttatus		GD	-D	EA	-D	DS					
S	camelus		GD	-D	EA	-D	DS					
C	coturnix		GD	-D	EA	-D	DS					
G	gallus		GD	-D	EA	-D	DS					
A	platyrhynch		GD	-D	EA	-D	ES					
A	fuligula		GD	-D	EA	-D	ES					
A	chrysaetos		GD	-D	EA	-D	DS					
F	cherrug		GD	-D	EA	-D	DS					
C	anna		GD	-D	EA	-D	DS					
C	livia		GD	-D	EA	-D	DS					
C	vociferus		GD	-D	EA	-D	DS					
N	nippon		GD	-D	EA	-D	DS					
C	canorus		GD	-D	EA	-D	DS					
M	undulatus		GD	-D	EA	-D	DS					
P	filicauda		PE	TE	EA	GE	DS					
N	chrysocepha		PE	TE	EA	GE	DS					
F	albicollis		PE	SE	EA	AE	DS					
C	moneduloid		PE	SE	EA	TE	DS					
P	major		TE	SE	EA	TE	DS					
T	guttata		PE	SE	EA	TE	ES					
L	striata		PE	SE	EA	TE	ES					
P	humilis		TE	SE	EA	AE	DS					
Z	albicollis		AE	-E	EA	-E	DS					
P	muralis		GD	-D	EA	-D	DS					
A	carolinensis		GD	-D	EA	-D	DS					
P	vitticeps		GD	-D	EA	-D	DS					
T	elegans		AH	EH	DA	AH	ES					
P	mucrosqua		-D	-D	DA	-D	DS					
C	mydas		GD	-D	EA	-D	ES					

Supp. Fig. 4O



Supp. Fig. 4P



Supp. Fig. 4Q

γ-syn. βIVa-tub.

Correlated pairs

Genus	species	protein	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a
		residue	58	443	46	316	64
		Z-score	6.5	6.5	5.9	5.9	5.9
H	sapiens		KV	EV	VV	KV	VV
P	troglodytes		KV	EV	VV	KV	VV
P	paniscus		KV	EV	VV	KV	VV
G	gorilla		KV	EV	VV	KV	VV
P	abelii		KV	EV	VV	KV	VV
H	moloch		KV	EV	VV	KV	VV
N	leucogenys		KV	EV	VV	KV	VV
P	anubis		KV	EV	VV	KV	VV
M	leucophaeu		KV	EV	VV	KV	VV
C	atys		KV	EV	VV	KV	VV
M	nemestrina		KV	EV	VV	KV	VV
M	mulatta		KV	EV	VV	KV	VV
M	fascicularis		KV	EV	VV	KV	VV
C	sabaeus		KV	EV	VV	KV	VV
T	gelada		KV	EV	VV	KV	VV
P	tephroscele		KV	EV	VV	KV	VV
R	bieti		KV	EV	VV	KV	VV
R	roxellana		KV	EV	VV	KV	VV
C	capucinus		KV	EV	VV	KV	VV
S	boliviensis		KV	EV	VV	KV	VV
S	apella		KV	EV	VV	KV	VV
C	jacchus		KV	EV	VV	KV	VV
A	nancymaae		KV	EV	VV	KV	VV
P	coquereli		KV	EV	VV	KV	VV
M	murinus		KV	EV	VV	KV	VV
O	garnettii		KV	EV	VV	KV	VV
T	chinensis		KV	EV	VV	KV	VV
D	ordii		KV	EV	VV	KV	VV
J	jaculus		KV	EV	VV	KV	VV
M	flaviventris		KV	EV	VV	KV	VV
M	marmota		KV	EV	VV	KV	VV
I	tridecemlin		KV	EV	VV	KV	VV
F	damarensis		KV	EV	VV	KV	VV
C	lanigera		KV	EV	VV	KV	VV
O	degus		KV	EV	VV	KV	VV
N	galili		KV	EV	VV	KV	VV
H	glaber		KV	EV	VV	KV	VV
M	ochrogaster		KV	EV	VV	KV	VV

Correlated pairs

Genus	species	protein	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a
		residue	58	443	46	316	64	5	64	74	64
C	griseus		KV	EV	VV	KV	VV
M	unguiculatu		KV	EV	VV	KV	VV
P	maniculatus		KV	EV	VV	KV	VV
M	auratus		KV	EV	VV	KV	VV
R	norvegicus		KV	GV	VV	KV	VV
M	pahari		KV	EV	VV	KV	VV
M	caroli		KV	EV	VV	KV	VV
M	musculus		KV	EV	VV	KV	VV
O	princeps		KV	EV	VV	KV	VV
O	cuniculus		KV	EV	VV	KV	VV
S	scrofa		KV	EV	VV	KV	VV
C	hircus		KV	EV	VV	KV	VV
O	aries		KV	EV	VV	KV	VV
O	virginianus		KV	EV	VV	KV	VV
B	taurus		KV	EV	VV	KV	VV
B	mutus		KV	EV	VV	KV	VV
B	bubalis		KV	EV	VV	KV	VV
C	ferus		KV	EV	VV	KV	VV
B	acutorostrat		KV	EV	VV	KV	VV
L	obliquidens		KV	EV	VV	KV	VV
G	melas		KV	EV	VV	KV	VV
O	orca		KV	EV	VV	KV	VV
P	sinus		KV	EV	VV	KV	VV
N	asiaeorienta		KV	EV	VV	KV	VV
D	leucas		KV	EV	VV	KV	VV
M	monoceros		KV	EV	VV	KV	AV
L	vexillifer		KV	EV	VV	KV	VV
C	simum		KV	EV	VV	KV	VV
E	asinus		KV	EV	VV	KV	VV
E	caballus		KV	EV	VV	KV	VV
L	canadensis		KV	EV	VV	KV	VV
F	catus		KV	EV	VV	KV	VV
A	jubatus		KV	EV	VV	KV	VV
P	vitulina		KV	EV	VV	KV	VV
L	weddellii		KV	EV	VV	KV	VV
N	schauinslan		KV	EV	VV	KV	VV
O	rosmarus		KV	EV	VV	KV	IV
Z	californianu		KV	EV	VV	KV	VV

Correlated pairs

Genus	species	protein	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a
		residue	58	443	46	316	64	5	64	74	64
U	arctos		KV	EV	VV	KV	VV
M	putorius		KV	EV	VV	KV	VV
M	erminea		KV	EV	VV	KV	VV
C	lupus		KV	EV	VV	KV	IV
M	javanica		KV	EV	VV	KV	VV
P	discolor		KV	EV	VV	KV	VV
H	armiger		KV	EV	VV	KV	VV
M	natalensis		KV	EV	VV	KV	VV
E	fuscus		KV	EV	VV	KV	VV
M	brandtii		KV	EV	VV	KV	VV
R	aegypticus		KV	EV	VV	KV	VV
C	cristata		KV	EV	VV	KV	VV
S	araneus		KV	EV	VV	KV	VV
E	europaeus		KV	EV	VV	KV	VV
C	aslatica		KV	EV	VV	KV	VV
D	novemcinct		KV	EV	AV	RV	VV
S	harrisii		KV	EV	VV	KV	VV
V	ursinus		KV	EV	VV	KV	VV
P	cinereus		KV	EV	VV	KV	VV
O	anatinus		KV	EV	VV	KV	VV
A	sinensis		KV	EV	VV	KV	VV
A	mississippie		KV	EV	VV	KV	VV
P	muralis		KV	EV	VV	KV	VV
A	carolinensis		KV	EV	VV	KV	VV
P	vitticeps		KV	EV	VV	KV	VV
P	bivittatus		KV	EV	VV	KV	VV
P	mucrosqua		KV	EV	VV	KV	VV
T	carolina		KV	EV	VV	KV	VV
C	picta		KV	EV	VV	KV	VV
X	tropicalis		KV	EV	VV	KV	VV
X	laevis		KI	EI	VV	KV	VV
R	bivittatum		KV	EV	VV	KV	VV
M	unicolor		KV	EV	VV	KV	AV
G	seraphini		KV	EV	VV	KV	VV
L	chalumnae		KV	EV	AI	MI	AI
E	calabaricus		KV	EV	VI	KI	AI
L	oculatus		KV	EV	VI	KI	AI
P	kingsleyae		KV	EV	VI	KI	AI

Correlated pairs

Genus	species	protein	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a	γ5 4a
		residue	58	443	46	316	64	5	64	74	64
S	formosus		KV	EV	VI	KI	AI
A	mexicanus		KV	EV	VI	KI	AI
P	nattereri		KV	EV	VI	KI	AI
D	clupeoides		KV	EV	VI	KI	AI
P	hypophthal		KV	EV	VI	KI	AI
D	rerio		KV	EV	VI	KI	AI
S	rhinoceros		KV	EV	VI	KI	AI
E	electricus		KV	EV	VI	KI	AI
I	punctatus		KA	EA	VI	KI	AI
T	fulvidraco		KV	EV	VI	KI	AI
S	salar		RA	DA	VI	KI	AI
S	trutta		RA	DA	VI	KI	AI
O	mykiss		RA	DA	VI	KI	AI
O	kisutch		RA	DA	VI	KI	AI
P	formosa		KV	EV	AI	RI	AI
P	reticulata		KV	EV	VI	RI	AI
P	latipinna		KV	EV	AI	RI	AI
P	mexicana		KV	EV	AI	RI	AI
X	helleri		KV	EV	VI	RI	AI
X	couchianus		KV	EV	VI	RI	AI
X	maculatus		KV	EV	VI	RI	AI
C	variegatus		KV	EV	VI	RI	AI
T	rubripes		KV	EV	VI	KI	AI
M	armatus		KV	EV	VI	KI	AI
F	heteroclitus		KV	EV	VI	RI	AI
O	latipes		KV	EV	VI	KI	AI
A	testudineus		KV	EV	VI	KI	AI
B	splendens		KV	EV	VI	KI	AI
O	niloticus		KV	EV	VI	KI	AI
H	burtoni		KV	EV	VI	KI	AI
M	zebra		KV	EV	VI	KI	AI
L	bergylta		KV	EV	VI	KI	AI
S	lucioperca		KV	EV	VI	KI	AI
L	crocea		KV	EV	VI	KI	AI
C	milii		KV	EV	VV	KV	VV
S	torazame		KV	EV	VV	KV	VV

