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Global non-random abundance of short tandem repeats in rodents and primates.

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Abstract

Background: While of predominant abundance across vertebrate genomes and significant biological implications, the relevance of short tandem repeat (STR) abundance to speciation remains largely elusive and attributed to random coincidence for the most part. In a model study, here we collected whole-genome abundance of mono-, di-, and trinucleotide STRs in nine species, encompassing rodents and primates, including rat, mouse, olive baboon, gelada, macaque, gorilla, chimpanzee, bonobo, and human. The obtained unnormalized and normalized data were used to analyze hierarchical clustering of the STR abundances in the selected species.

Results: We found massive differential abundances between the rodent and primate orders. In addition, while numerous STRs had random abundance across the nine selected species, the global abundance conformed to three consistent <clusters>, as follows: <rat, mouse>, <gelada, macaque, olive baboon>, <gorilla, chimpanzee, bonobo, human>, which coincided with the phylogenetic distances of the selected species ($p < 4E-05$). Exceptionally, in the trinucleotide STR compartment, human was significantly distant from all other species.

Conclusion: We propose that the global abundance of STRs is non-random in rodents and primates, and probably had a determining impact on the speciation of the two orders. We also propose the STRs and STR lengths which specifically coincided with the phylogeny of the selected species.

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Introduction

With an exceptionally high degree of polymorphism and plasticity, short tandem repeats (STRs) (also known as microsatellites/simple sequence repeats) are a spectacular source of variation required for speciation and evolution[1-3]. The impact of STRs on speciation is supported by their various functional implications in gene expression, alternative splicing, and translation[3-10].

STRs are a source of rapid and continuous morphological evolution[11], for example, in the evolution of facial length in mammals[12]. These highly evolving genetic elements may also be ideal responsive elements to fluctuating selective pressures. A role in evolutionary selection and adaptation is consistent with deep evolutionary conservation of some STRs, as "tuning knobs", including several in genes with neurological and neurodevelopmental function[13].

While a limited number of studies indicate that purifying selection and drift can shape the structure of STRs at the inter- and intra-species levels [14-19], the global abundance of STRs at the crossroads of speciation remains largely unknown.

Mononucleotide and dinucleotide STRs are the most common categories of STRs in the vertebrate genomes[20, 21]. In addition to their association with frameshifts in coding sequences and pathological [22] and possibly evolutionary consequences, recent evidence indicates surprising functions for the mononucleotide STRs, such as their provisional role in translation initiation site selection[9]. Several groups have found evidence on the involvement of a number of dinucleotide STRs in gene regulation, speciation, and evolution[3, 20, 23-26]. Trinucleotide STRs are frequently linked to human neurological disorders, most of which are specific to this species[27, 28].

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In a model study, here we analyzed the evolutionary abundance of all types of mono-, di-, and trinucleotide STRs in nine selected species, encompassing rodents, Old World monkeys, and great apes.

Materials and Methods

Species and whole-genome sequences

By using the UCSC genome browser (https://hgdownload.soe.ucsc.edu), the whole genomes of nine species were downloaded and analyzed, species and genome sizes of which were as follows: rat (*Rattus norvegicus*): 2,647,915,728, mouse (*Mus musculus*): 2,728,222,451, gelada (*Theropithecus gelada*): 2,889,630,685, olive baboon (*Papio anubis*): 2,869,821,163, macaque (*Macaca mulatta*): 2,946,843,737, gorilla (*Gorilla gorilla gorilla*): 3,063,362,754, chimpanzee (*Pan troglodytes*): 3,050,398,082, bonobo (*Pan paniscus*): 3,203,531,224, and human (*Homo sapiens*): 3,099,706,404. Those species encompassed rodents: rat and mouse, Old World monkeys: gelada, olive baboon, macaque, and great apes: gorilla, bonobo, chimpanzee, human.

Extraction of STRs from genomic sequences

The whole-genome abundance of mononucleotide STRs of ≥10-repeats, dinucleotide STRs of ≥6-repeats, and trinucleotide STRs of ≥4-repeats were studied in the nine selected species. To that end, we designed a software package in Java (https://github.com/arabfard/Java_STR_Finder). All possibilities of mononucleotide motifs, consisting of A, C, T, and G, all possibilities of dinucleotide motifs, consisting of AC, AG, AT, CA, CG, CT, GA, GC, GT, TA, TC, and TG, and all possibilities of trinucleotide motifs, consisting of AAC, AAT, AAG, ACA, ACC, ACT, ACG, ATA, ATC, ATT, ATG, AGA, AGC,

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AGT, AGG, CAA, CAC, CAT, CAG, CCA, CCT, CCG, CTA, CTC, CTT, CTG, CGA, CGC, CGT, CGG, TAA, TAC, TAT, TAG, TCA, TCC, TCT, TCG, TTA, TTC, TTG, TGA, TGC, TGT, TGG, GAA, GAC, GAT, GAG, GCA, GCC, GCT, GCG, GTA, GTC, GTT, GTG, GGA, GGC, and GGT were analyzed. The written program was based on perfect (pure) STRs.

Chromosome-by-chromosome aggregation of STRs

Whole-genome chromosome-by-chromosome data were aggregated and analyzed in the nine species, without normalization (approach 1) and with normalization (approach 2). In approach 1, all chromosomal data were collected without removing any numerically non-identical chromosomes across the nine species. In approach 2, data on the identical chromosome sets (numerically) across the nine species were collected in an array of 20 columns, each column corresponding to a chromosome. In this approach, mouse was selected as reference, because it had the lowest number of chromosomes among the nine species.

STR abundance and hierarchical cluster analysis across species

Whole-genome STR abundances across the selected species were deciphered and depicted by boxplot diagrams and hierarchical clustering, using boxplot and hclust packages[29] in R, respectively. Boxplots illustrate abundance differences among segments across the selected species, and hierarchical clustering plots demonstrate the level of similarity and differences across the obtained abundances. The input data to these packages were numerical arrays obtained with each approach. Each array consisted of a number of columns, each column corresponding to the STR abundance in different chromosomes.

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Statistical analysis

The STR abundances across the nine selected species were compared by repeated measurements analysis, using one and two-way ANOVA tests. These analyses were confirmed by nonparametric tests.

Results

Global abundance of mono, di, and trinucleotide STRs coincides with the phylogenetic distance of the nine selected species.

Chromosome-by-chromosome data were collected on the abundance of mononucleotide STRs across the nine species (Table 1). We found massive expansion of the mononucleotide STR compartment in all primate species vs. rat and mouse. Hierarchical clustering yielded three <clusters> as follows: <rat, mouse>, <gelada, olive baboon, macaque>, and <gorilla, chimpanzee, bonobo, human>, which coincided with the phylogenetic distance of the nine selected species in both unnormalized (P=6.3E-09) (Fig. 1) and normalized approaches (P=1.4E-08) (Suppl. 1), namely <rodents>, <Old World monkeys>, and <great apes>.

The whole-genome STR abundances from aggregated chromosome-by-chromosome analysis in the dinucleotide category (Table 2) was decremented in primates vs. rodents. Similar to the mononucleotide STR compartment, the dinucleotide STR compartment coincided with the genetic distance among the three <clusters> of species with the unnormalized (P=7.1E-08) (Fig. 2) and normalized data (P=6.8E-11) (Suppl. 1).

There was global shrinkage of the trinucleotide STR compartment in primates vs. rodents, without (P=3.8E-05) and with normalization of the data (P=2.4E-07) (Table 3, Fig. 3 and Suppl. 1). Remarkably, human stood out among all other species in the hierarchical clustering,

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Differential abundance patterns of STRs across rodents and primates.

Numerous STRs across the mono, di, and trinucleotide STR categories coincided with the phylogenetic distances of the nine selected species. For example, the most abundant STRs across all nine species were T/A mononucleotides of 10, 11, and 12 repeats, which coincided with the genetic distance of the selected species (Fig. 4). Likewise, (ct)6 and (taa)4 conformed to the phylogeny of the studied species in the di and trinucleotide STR categories, respectively. On the other hand, numerous STRs did not follow a phylogenetic pattern, such as (C)10, (AT)8, and (ttg)4 (Fig. 5). Hierarchical clusters of all studied STRs across the three categories are available at: https://figshare.com/articles/figure/STR_Clustering/17054972.

Discussion

It is largely unknown whether at the crossroads of speciation, STRs evolved as a result of purifying selection, genetic drift, and/or in a directional manner. In a model study, we selected multiple species across rodents and primates, and investigated the abundance of all possible types of mononucleotides, dinucleotide, and trinucleotide STRs on the whole-genome scale in those species. Hierarchical clustering of the obtained abundances yielded clusters that predominantly coincided with the phylogenetic distances of the selected species.

Hierarchical clustering is an unsupervised clustering method that is used to group data. This algorithm is unsupervised because it uses random, unlabelled datasets. As the number of clusters increases, the accuracy of the hierarchical clustering algorithm improves. Here we implemented this algorithm to cluster the nine selected species based on the obtained STR abundances.

Our findings may be of significance in two respects. Firstly, there were significant differential abundances separating rodents from primates, for example, massive decremented abundance of

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dinucleotide and trinucleotide STRs in primates vs. the rodent species, and massive incremented abundance of mononucleotide STRs in primates vs. rodents. Those differential abundances might have determining roles in the speciation of the two orders. Secondly, the three major clusters obtained from global hierarchical cluster analysis matched the phylogeny of the three classes of species, i.e., <rodents>, <Old World monkeys>, and <great apes>. It is possible that there are mathematical channels/thresholds required for the abundance of STRs in various orders. This is in line with the hypothesis that STRs function as scaffolds for biological computers[30].

In addition, our data indicate that various STRs and STR lengths behave differently with respect to their colossal abundance. Not all studied STRs coincided with the phylogenetic distances of the nine selected species. We hypothesize that those which coincided had a link with the speciation of those species, whereas those which did not probably followed random patterns. The obtained abundances seem to be independent of the genome sizes of the selected species, for example in the instances of di- and trinucleotide STRs. This finding is in line with the previous reports of lack of relationship between genome size and abundance of STRs[14, 31, 32]. Mononucleotide STRs impact various processes, such as gene expression and translation alterations and frameshifts of various proteins, which may have evolutionary and pathological consequences[9, 22]. They can overlap with G4 structures, many of which associate with evolutionary consequences[33].

Dinucleotide STRs located in the protein-coding gene core promoters have been subject to contraction in a number of instances, in the process of human and non-human primate evolution[34]. A number of those STRs are identical in formula in primates vs. non-primates, and the genes linked to those STRs are involved in characteristics that have diverged primates

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from other mammals, such as craniofacial development, neurogenesis, and spine morphogenesis. It is likely that those STRs functioned as evolutionary switch codes for primate speciation. In line with the above, structural variants are enriched near genes that diverged in expression across great apes[35], and genes with STRs in their regulatory regions were more divergent in expression than genes with fixed or no STRs[36]. It is speculated that STR variants are more likely than single-nucleotide variants to have epistatic interactions, which can have significant consequences in complex traits, in human as well as model organisms[37, 38]. Trinucleotide STRs are predominantly focused on in human because of their link with several neurological disorders[39-44]. Intriguingly, we found an exceptional global hierarchical distance between human and all other species. In view of the fact that most of the phenotypes attributed to trinucleotide STRs are human-specific in nature, it is conceivable that their evolution is also significantly distant from all other species studied.

Future studies such as large-scale genome-editing of STRs[45] in embryonic stem cells and investigation of their differentiation into various cell lineages may be candidate approaches to investigate how the observed massive non-random patterns link to speciation and evolution.

Conclusion

We propose that the global abundance of STRs is non-random across rodents and primates. We also propose the STRs and STR lengths which coincided with the phylogenetic distances of those species.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

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Not applicable

Availability of data and materials

Raw data are available at: https://figshare.com/articles/dataset/Trends/15073329 and https://figshare.com/articles/figure/STR_Clustering/17054972

Competing interests

Authors have no conflict of interest to declare.

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Authors' contributions

MA performed and coordinated the bioinformatics analyses. MS performed the biostatistics analysis. YHN, IA, and AMAM contributed to data collection. KK contributed to data collection and coordination. MO conceived and supervised the project, and wrote the manuscript.

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Figures

Fig. 1. Unnormalized data on whole-genome mononucleotide STRs in the nine selected species. Global incremented pattern was observed in the primate species vs. rodents (left graphs). The

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overall hierarchical clustering yielded three clusters, which coincided with rodents, Old World monkeys, and great apes (right graphs).

Fig. 2. Unnormalized data on whole-genome dinucleotide STRs in the nine selected species. Global decremented patterns were observed in all primate species vs. mouse and rat.

Fig. 3. Unnormalized data on whole-genome trinucleotide STRs in the nine selected species. While global decremented patterns were observed in primates vs. rodents, intriguingly, human stood out in this category, in comparison to all other species.

Fig. 4. Example of STRs and STR lengths, abundance of which coincided with the phylogeny of the nine selected species. Three STRs are depicted as examples for each of mono, di, and trinucleotide categories. Data from all studied STRs are available at: https://figshare.com/articles/figure/STR_Clustering/17054972.

Fig. 5. Example of STRs and STR lengths, abundance of which appeared to be random across the nine selected species. Three STRs are depicted as examples for each of mono, di, and trinucleotide categories. Data from all studied STRs are available at: https://figshare.com/articles/figure/STR_Clustering/17054972.

Suppl. 1. Normalized data across the nine selected species.

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Table 1. Whole-genome mononucleotide STR abundance. Chromosome-by-chromosome data across the nine selected species.

Chromosome/Species	Rat	Mouse	Gelada	Baboon	Macaque	Gorilla	Chimpanzee	Bonobo	Human
1	53318	47294	90549	87241	83595	77718	79390	79173	82820
2(A)	46221	45636	71588	67963	64609	35908	35897	34400	78550
2(B)	0	0	0	0	0	40245	39968	39837	0
3	36364	38493	70736	68688	65836	62398	62713	64472	64027
4	34818	39019	62831	60726	57817	54896	54855	53287	56495
5	36532	38805	66164	64101	61533	60436	48944	54142	56538
6	28617	35751	63104	61642	59150	53872	53769	53420	55185
7(A)	29411	33649	25699	65267	63438	50898	53882	50792	56257
7(B)	0	0	42663	0	0	0	0	0	0
8	27353	31938	50576	48446	46757	43593	44212	43618	45220
9	23532	31142	50050	47879	46910	36797	38035	37493	41744
10	31065	34138	41475	39012	37477	44166	44562	44416	46075
11	17071	33869	54287	54284	51654	37218	41059	40757	42217
12	15101	29325	42675	35365	42793	46865	47576	47481	48483
13	21673	29496	40602	39101	38022	27902	28481	28479	29430
14	21835	28835	45820	44693	42677	30311	30659	30595	31460
15	20351	25753	43334	41671	40009	28611	29752	29049	31402
16	15958	24139	41211	39781	37693	29268	31121	28460	34364
17	18458	24234	32308	31285	30378	29884	36791	37010	38947
18	16651	22580	25310	24850	23551	22556	22428	22236	23130
19	14266	16221	35819	32702	30470	23832	31405	30614	32423
20	14475	0	34962	32965	32095	20654	22106	31034	21961
21	0	0	0	0	0	10462	10633	10467	12050
22	0	0	0	0	0	13778	14816	13904	16014
X	25983	40547	52836	49013	47590	43138	43302	41656	46178
Sum	**549053**	**650864**	**1084599**	**1036675**	**1004054**	**925406**	**946356**	**946792**	**990970**

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Table 2. Whole-genome dinucleotide STR abundance. Chromosome-by-chromosome data across the nine selected species.

Chromosome/Species	Rat	Mouse	Gelada	Baboon	Macaque	Gorilla	Chimpanzee	Bonobo	Human
1	81509	59425	24335	23427	24462	23105	23708	23583	24657
2(A)	74837	53096	21315	20302	21225	11820	11960	11391	26989
2(B)	0	0	0	0	0	14494	14555	14334	0
3	53642	45464	20710	19973	20552	20939	21179	21039	21633
4	57299	44963	19364	18592	19038	21536	21182	20503	21773
5	52269	48069	22020	21275	22147	17099	17831	19606	20385
6	44993	45325	19921	19397	20070	18575	18391	18196	18995
7(A)	43219	40052	5832	16963	17870	15988	16727	16130	17275
7(B)	0	0	11934	0	0	0	0	0	0
8	43242	41103	15903	15390	16164	15837	15875	15718	16245
9	37463	39005	14733	14183	14857	11704	11935	11661	13080
10	40260	40998	10136	9432	9855	14051	14306	14032	14799
11	27685	38212	14360	14487	15187	12678	13988	13842	14189
12	22084	35361	13478	14325	14685	14385	14559	14588	14757
13	38331	35159	11839	11292	11797	11071	11258	11135	11406
14	31923	36644	13605	13243	13885	9549	9465	9386	9798
15	31768	30662	12078	11661	12014	8014	8226	8143	8607
16	28704	29521	8228	8064	8206	7814	8268	7553	8947
17	30312	28209	11002	10457	10942	10456	8056	8006	8355
18	27797	27263	8548	8349	8591	8629	8597	8497	8750
19	21794	18350	5994	5493	5395	4774	6081	5865	6220
20	20191	0	8334	7902	8345	6379	7106	6623	6612
21	0	0	0	0	0	4092	4154	4123	4884
22	0	0	0	0	0	3209	3442	3183	3746
X	36246	38470	18303	16787	17659	17922	18193	17078	18952
Sum	**845568**	**775351**	**311972**	**300994**	**312946**	**304120**	**309042**	**304215**	**321054**

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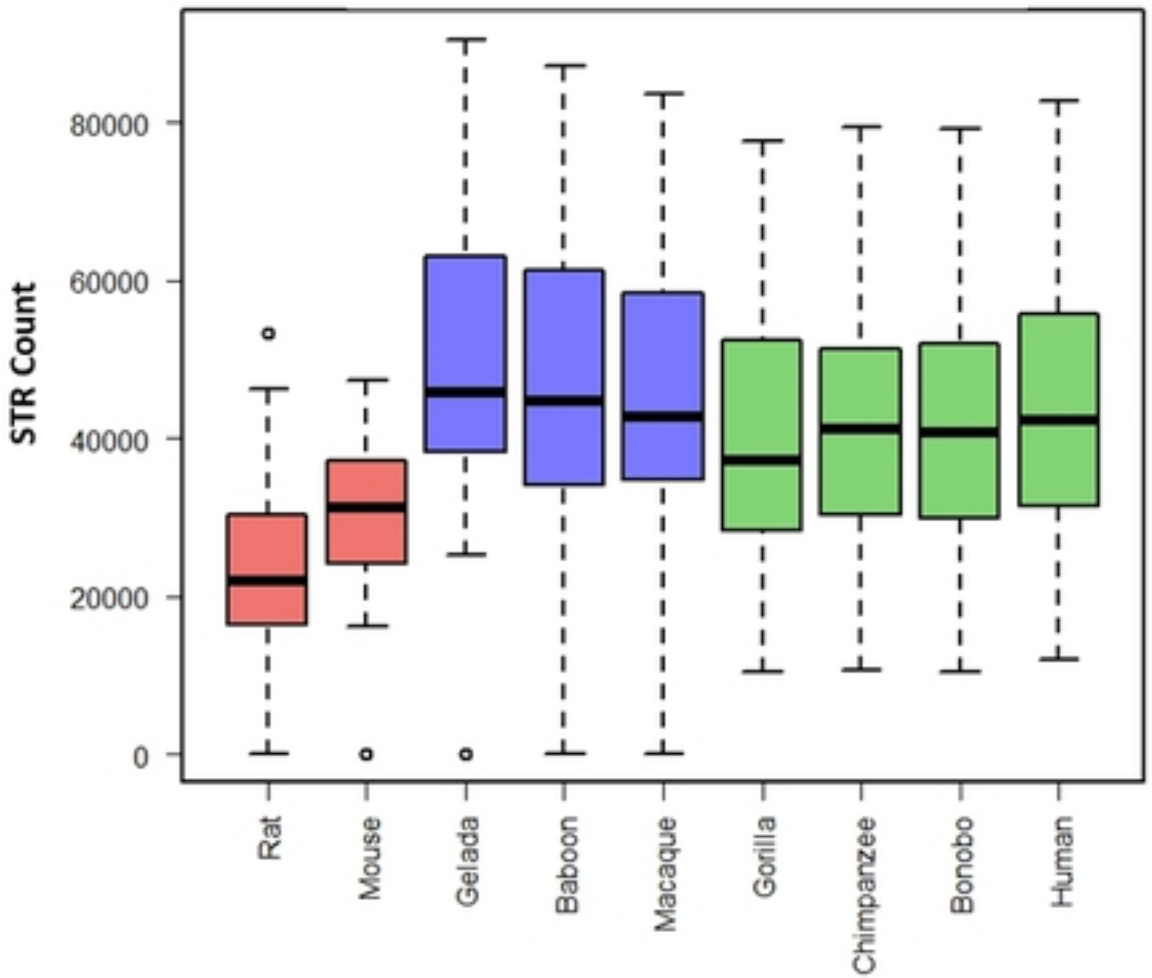
Table 3. Whole-genome trinucleotide STR abundance. Chromosome-by-chromosome data across the nine selected species.

Chromosome/Species	Rat	Mouse	Gelada	Baboon	Macaque	Gorilla	Chimpanzee	Bonobo	Human
1	25234	18913	16307	15350	15341	14540	15219	15054	14882
2(A)	22996	17856	13005	12341	11998	6800	6842	6537	14521
2(B)	0	0	0	0	0	7545	7764	7822	0
3	16869	15022	12749	12518	11938	11473	11744	11637	11631
4	17088	15204	11921	11154	10960	11116	11228	10685	11144
5	16339	15469	13001	12514	12112	10581	9665	10640	10649
6	13495	14332	12150	11743	11380	10364	10504	10445	29430
7(A)	14317	13760	3937	10991	10871	9342	10117	9744	9995
7(B)	0	0	7552	0	0	0	0	0	0
8	12701	13518	10032	9524	9682	8752	9096	8645	8890
9	11646	12378	9295	8755	8659	6898	7328	7157	7580
10	12552	13968	7297	6728	6786	8096	8350	8245	8295
11	7987	13232	9615	9578	9403	7801	8668	8458	8352
12	6060	11817	7742	8297	8029	8905	9218	9051	9127
13	10852	11634	7266	6823	6860	5273	5479	5452	5391
14	10325	11865	8869	8583	8253	5473	5771	5785	5706
15	10075	10693	7727	7339	7152	4869	5168	5082	5297
16	8476	9527	6228	5837	5801	5738	6007	5623	6402
17	9502	10045	5908	5737	5684	5666	5859	5914	6091
18	8124	9154	4738	4645	4603	4722	4625	4584	4566
19	6984	6190	5432	4643	4664	3807	5438	5230	5101
20	6445	0	6655	6016	5945	4072	4472	4155	4130
21	0	0	0	0	0	2051	2092	2028	2304
22	0	0	0	0	0	2721	2825	2601	2915
X	10411	13783	11449	10609	10666	9547	9838	9140	10062
Sum	**258478**	**258360**	**198875**	**189725**	**186787**	**176152**	**183317**	**179714**	**202461**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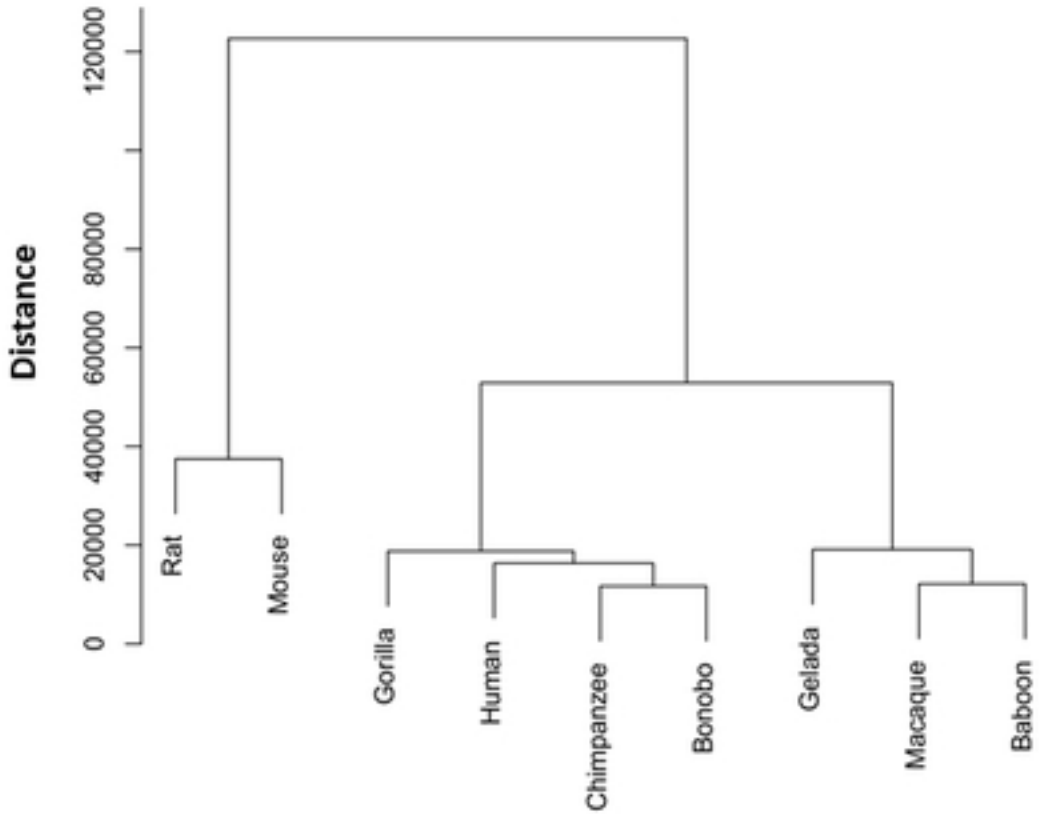
40000
60000
80000
Rat
Mouse
Gelada
Baboon
Macaque
Gorilla
Chimpanzee
Bonobo
Human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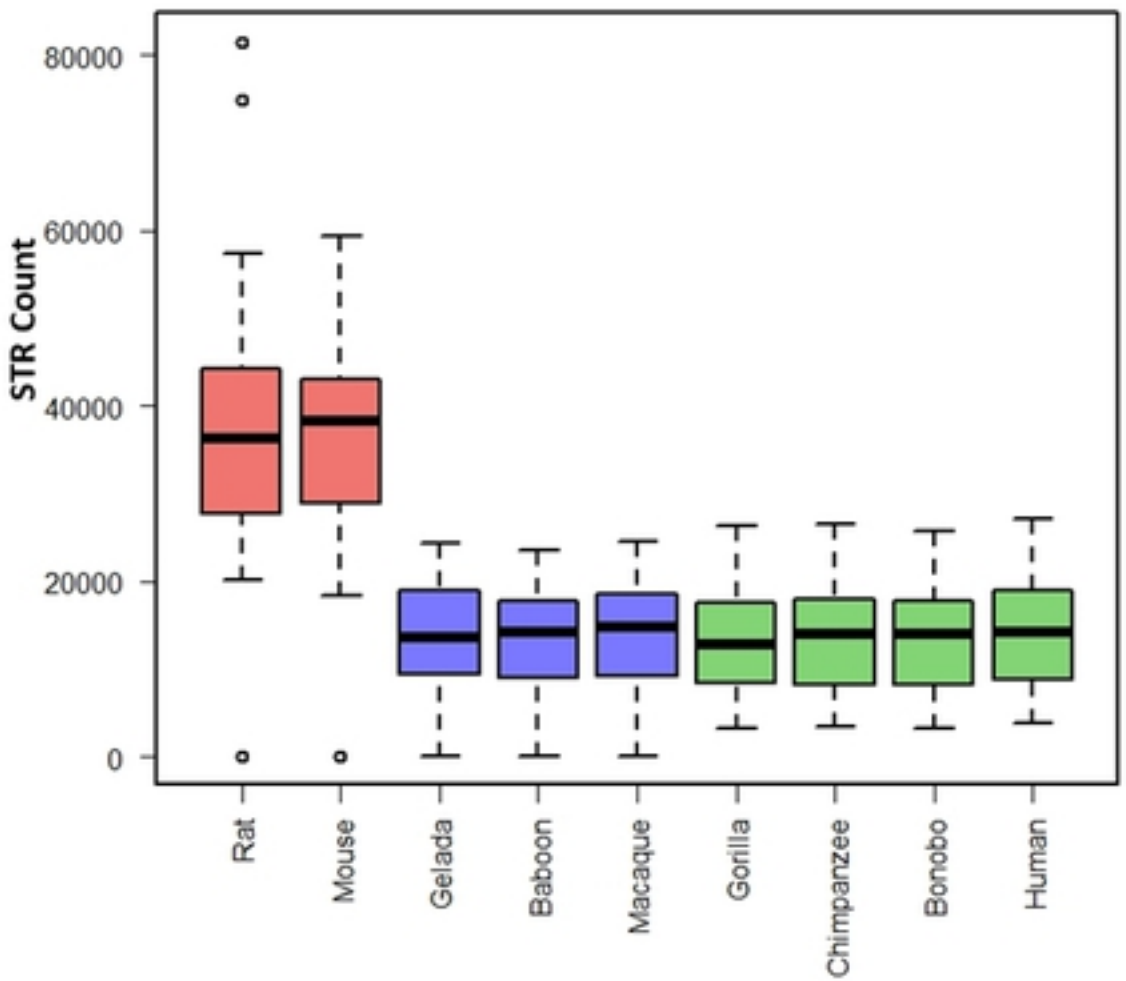
20000
40000
60000
80000
120000
Rat
Mouse
Gorilla
Human
Chimpanzee
Bonobo
Gelada
Macaque
Baboon

Fig. 1.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20000
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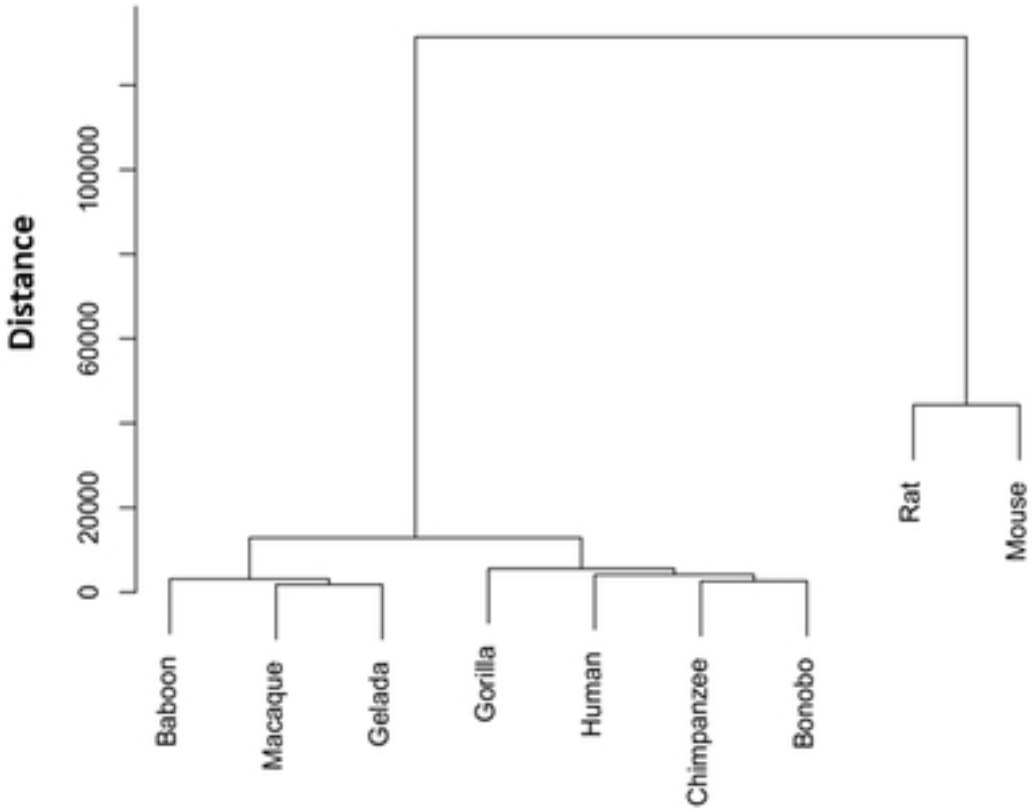
Rat
Mouse
Gelada
Baboon
Macaque
Gorilla
Chimpanzee
Bonobo
Human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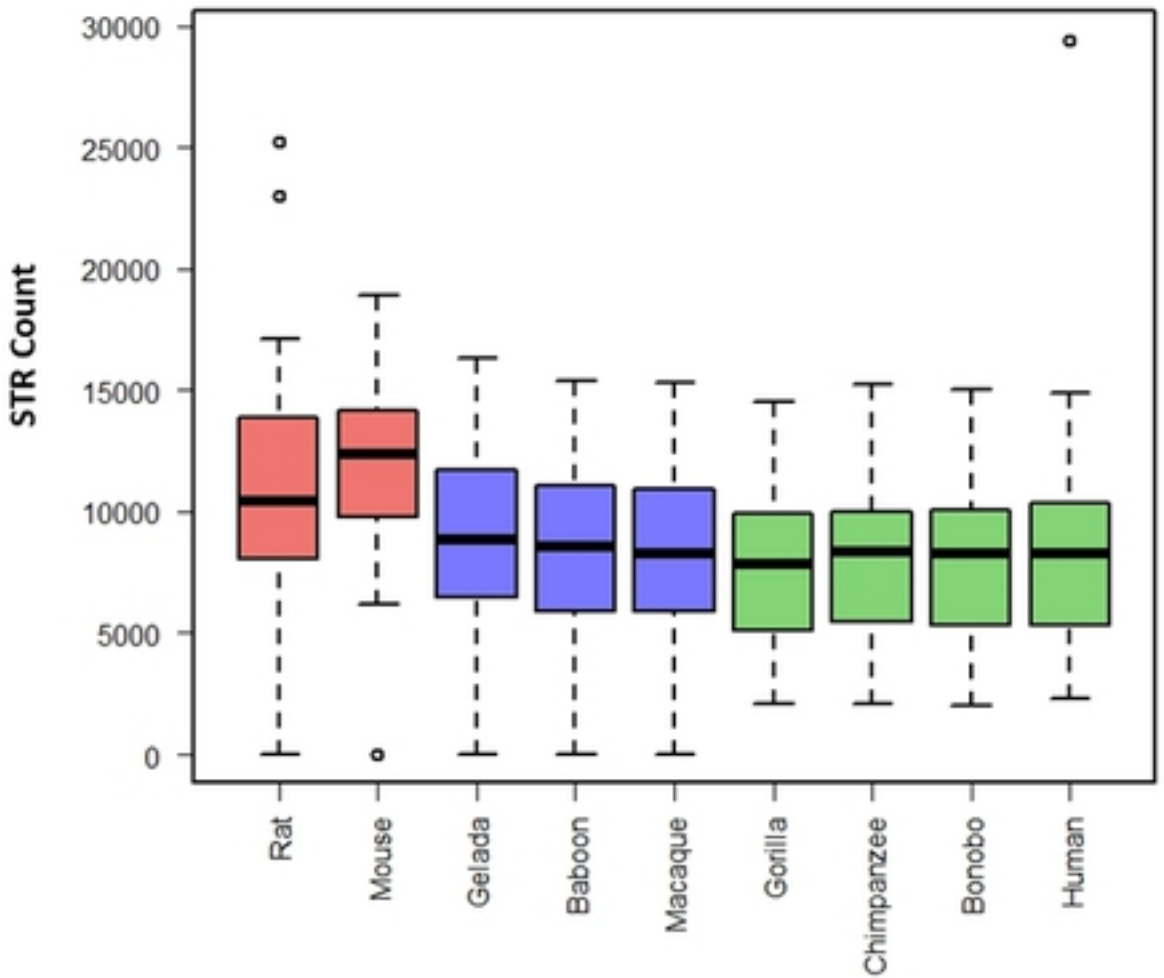
Baboon
Macaque
Gelada
Gorilla
Human
Chimpanzee
Bonobo
Rat
Mouse

Fig. 2.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10000
5000
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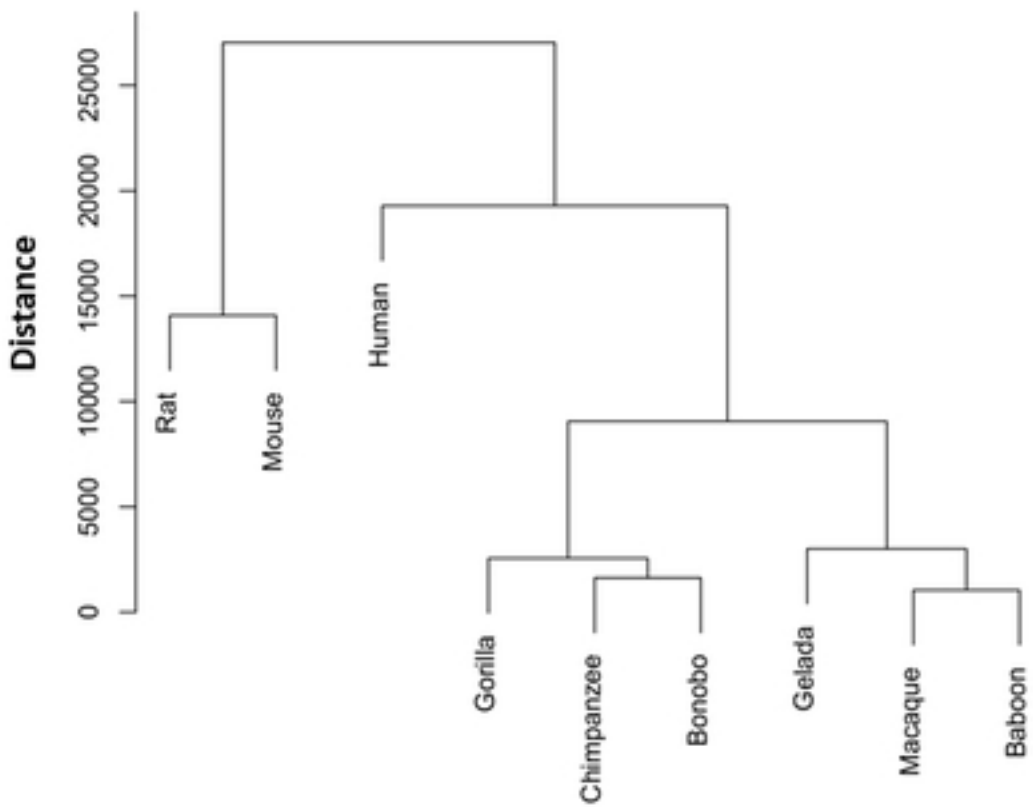
Rat
Mouse
Gelada
Baboon
Macaque
Gorilla
Chimpanzee
Bonobo
Human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10000
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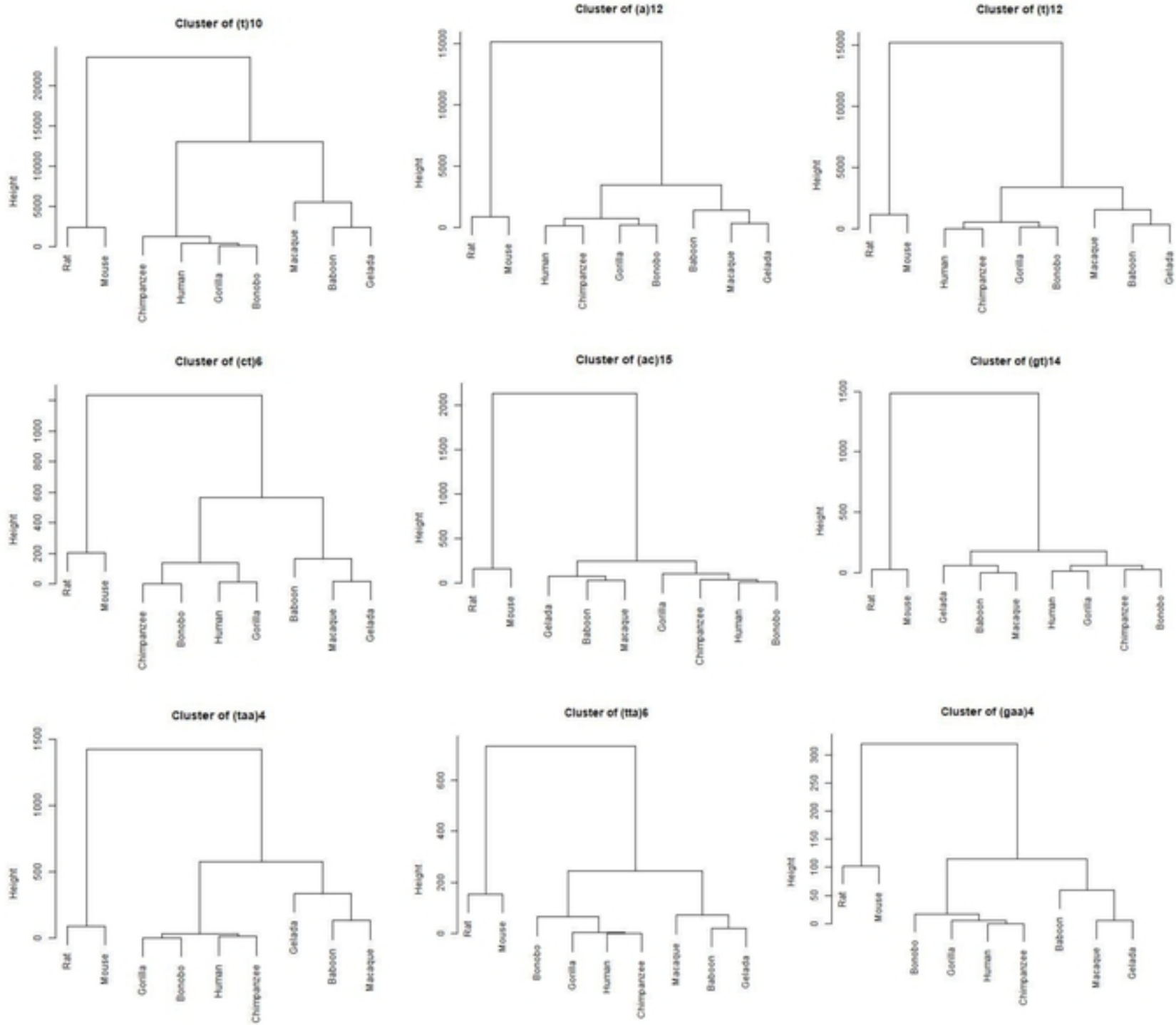
20000
25000
Rat
Mouse
Human
Gorilla
Chimpanzee
Bonobo
Gelada
Macaque
Baboon

Fig. 3.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10000
15000
20000
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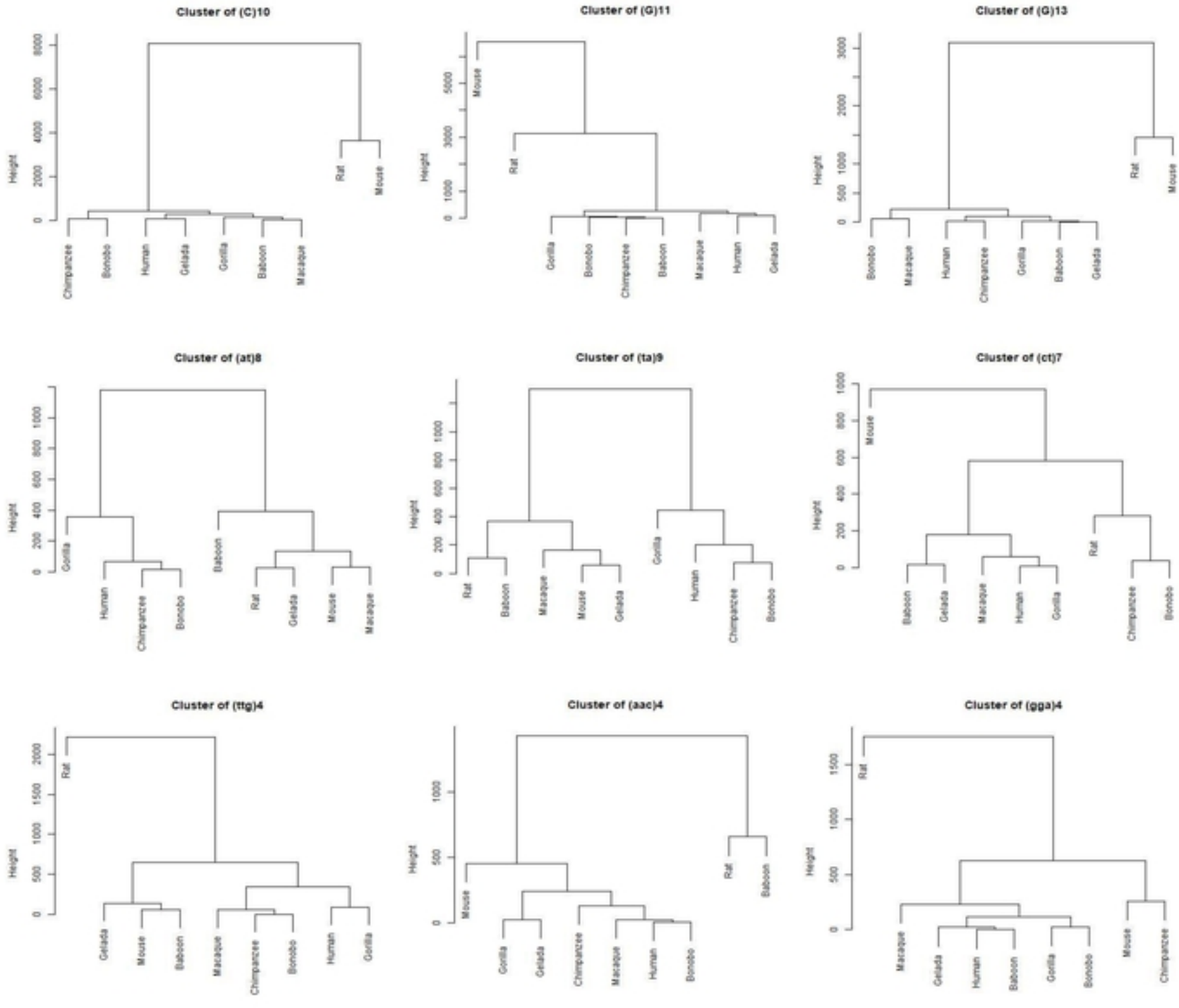
Mouse
Chimpanzee
Human
Gorilla
Bonobo
Macaque
Baboon
Gelada
Cluster of (a)12
Height
0
5000
10000
15000
Rat
Mouse
Human
Chimpanzee
Gorilla
Bonobo
Baboon
Macaque
Gelada
Cluster of (t)12
Height
0
5000
10000
15000
Rat
Mouse
Human
Chimpanzee
Gorilla
Bonobo
Macaque
Baboon
Gelada
Cluster of (ct)6
Height
0
200
400
600
800
1000
Rat
Mouse
Chimpanzee
Bonobo
Human
Gorilla
Baboon
Macaque
Gelada
Cluster of (ac)15
Height
0
500
1000
1500
2000
Rat
Mouse
Gelada
Baboon
Macaque
Gorilla
Chimpanzee
Human
Bonobo
Cluster of (gt)14
Height
0
500
1000
1500
Rat
Mouse
Gelada
Baboon
Macaque
Human
Gorilla
Chimpanzee
Bonobo
Cluster of (taa)4
Height
0
500
1000
1500
Rat
Mouse
Gorilla
Bonobo
Human
Chimpanzee
Gelada
Baboon
Macaque
Cluster of (tta)6
Height
0
200
400
600
Rat
Mouse
Bonobo
Gorilla
Human
Chimpanzee
Macaque
Baboon
Gelada
Cluster of (gaa)4
Height
0
50
100
150
200
250
300
Rat
Mouse
Bonobo
Gorilla
Human
Chimpanzee
Baboon
Macaque
Gelada

Fig. 4.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2000
4000
6000
8000
Chimpanzee
Bonobo
Human
Gelada
Gorilla
Baboon
Macaque
Rat
Mouse
Cluster of (G)11
Height
0
1000
3000
5000
Mouse
Rat
Gorilla
Bonobo
Chimpanzee
Baboon
Macaque
Human
Gelada
Cluster of (G)13
Height
0
500
1000
2000
3000
Rat
Mouse
Bonobo
Macaque
Human
Chimpanzee
Gorilla
Baboon
Gelada
Cluster of (at)8
Height
0
200
400
600
800
1000
Gorilla
Human
Chimpanzee
Bonobo
Baboon
Rat
Gelada
Mouse
Macaque
Cluster of (ta)9
Height
0
200
400
600
800
1000
Rat
Baboon
Macaque
Mouse
Gelada
Gorilla
Human
Chimpanzee
Bonobo
Cluster of (ct)7
Height
0
200
400
600
800
1000
Mouse
Rat
Baboon
Gelada
Macaque
Human
Gorilla
Chimpanzee
Bonobo
Cluster of (ttg)4
Height
0
500
1000
1500
2000
Rat
Gelada
Mouse
Baboon
Macaque
Chimpanzee
Bonobo
Human
Gorilla
Cluster of (aac)4
Height
0
500
1000
Mouse
Rat
Baboon
Gorilla
Gelada
Chimpanzee
Macaque
Human
Bonobo
Cluster of (gga)4
Height
0
500
1000
1500
Rat
Macaque
Gelada
Human
Baboon
Gorilla
Bonobo
Mouse
Chimpanzee

Fig. 5.