Creativity in Higher Education: Comparative Genetic Analyses on the Dopaminergic System in Relation to Creativity, Addiction, Schizophrenia in Humans and Non-Human Primates

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ABSTRACT

Teaching creativity is a substantial quality improvement in higher education. To demonstrate cross-functional thinking is a must for degree holders to be able to solve solutions useful for the society. Such a demand must be underlined by rational arguments. The neurobiology of creative behavior provides important information how the brain processes such activities. The subcortical mesolimbic brain areas, specifically the dopaminergic system, are of interest. The mentioned system and its two class receptors, D1 and D2 types, seem to be key players to mediate pleasure associated with predictive, motivational, or attentional sensations linked to learning processes and creativity. In this work a comparative biological approach was used to analyze genetic polymorphisms of SNPs in humans and nonhuman primates based on phenotypical expressions of creativity in humans. This methodology was used to get a view of the phylogenetic dimension of this trait in the order of primates. 13 out of 50 chosen SNPs showed accelerated selection processes shared by humans and non-human primates. The results of this study confirmed the assumption that phenotypical expression of creativity is a genetically inherited feature in primates. It is suggested that such a phylogenetic approach justifies a consideration of teaching creativity in higher education. It is suggested that creativity represents an old trait in primates because the most distant relative primate used in this study diverged 25 Mya ago from humans.

Keywords: Higher Education, Creativity, Neurobiology, Genetic Polymorphism, Humans, Non-Human Primates

1. INTRODUCTION

In the proceedings of The 8th International Multi-Conference on Complexity, Informatics and Cybernetics (IMCIC 2017) we claimed, that the process of creating quality in research and teaching affairs requires more than the definition of controlling variables or the desire to harmonize study programs. To teach creativity has to be a part of the quality management in universities [1]. At this stage of university education, teacher have the obligation to teach people to be able to apply creative solutions to solve recent and future problems. Takeuchi et al. [2] point out, "… creative potential measured by divergent thinking (CPMDT) is associated with individual differences in perspectives of emotion, mood and motivation … creativity has been traditionally and essentially linked to motivation …". This quote is the bridge to the neurobiology of creativity in humans and non-human primates. In humans, research on the dopaminergic system in relation to creativity focuses the creative potential, emotional intelligence corroborated with the risk of bipolar disorder and schizophrenia [2, 3, 4].

Before the biological details of the recent work will be outlined, the authors will illustrate how exclusive the "club" of students in the tertiary education sector is.

To receive a university education is globally the most desirable and expansive educational training individuals can achieve. The distribution of academically trained people within countries is extremely skewed and differs therefore, in numbers. Altbach and colleagues [5] present data from students enrolled in the tertiary education system in their publication entitled *tracking a global academic revolution.* For 2007 they showed a worldwide

number of tertiary students of approximately 150 million. The world population in 2007 was approximately 6.661 billion people [6]. At that time 2.2% of the world population represented students in higher education. We can find the lowest participation rates in traditional age cohorts of students in Sub-Saharian Africa, Arab states, and Southwest Asia and the highest numbers in western industrialized countries. The authors compared these numbers from 2007 with numbers from 2000 and reported an increase of more than 50% of students during that period. The data were provided by the UNESCO and for detailed information and future trends see [7]. Obviously, for many people it is not easy to get access to the post-secondary education system. Recently in Austria, 2016–17, 280,783 students enrolled in public universities, off 75,741 are from abroad [8]. In 2016, the total population in Austria was 8,739,806 people. A calculation of the students' proportion in relation to the total population of Austria revealed the same percentage of students, namely 2.3%, as outlined worldwide for 2007 [9]. Further, in 2016, Austrian public universities generated 34,539 academics, off 8,464 are from abroad. According to the total number of the population this is a fairly low number of people finishing their tertiary education. Consequential, the higher the degree of graduation the fewer individuals are finishing a PhD. The reasons for such a cone effect can be multiple. A very serious one is the "inheritance" of higher education. Offspring from higher educated parents have a better probability to receive a university education compared to those having less educated parents [10]. Anyway, those who are able to climb up the ladder of higher education and finish it are privileged, because after graduation they earn more money, live a healthier life and consequently live longer than the average individual of a population [11]. On the other hand, men who finish only a low level education, earn less money, are more frequently unmarried and have a decreased reproductive success at all [12]. These arguments do underline that a sociological issue such as education influences the biology of people and the trajectory of their life history. Based on the mentioned numbers in relation to the benefits of higher educated individuals one can argue that the quality of higher education has to be high as well, because degree holder have to give back benefits to the society. To teach creativity in a normative way based on methodological paradigms is certainly a possibility to increase teaching quality. But what justifies selecting creativity as a part of higher education – simply, it is an inherited biological trait.

The behavior creativity is evolutionarily rooted in the dopaminergic system – a part of the mesolimbic reward system – and one of the best-investigated brain areas in medicine and biology. Comparative studies on fishes, amphibians, reptiles, and mammals revealed homologous functional neuro-anatomic structures [13]. Therefore, these brain areas represent phylogenetically very old structures in vertebrates.

The monoamine neurotransmitter dopamine and its two class receptor system are key players in these subcortical structures to mediate pleasure associated with predictive, motivational, or attentional sensations in relation to learning processes [13, 14, 15, 16, 17]. The dopaminergic system is linked to the prefrontal cortex to mediate cognitive processes, which connect emotional and behavioral states [18, 19]. Comparative analyses of cortical dopaminergic innervation among humans and non-human primates reveal no quantitative differences between chimpanzees, macaques and humans. However, neocortical sublaminar patterns of innervation differed in specific areas between humans and the other two species [20].

In humans the cortical cognition of pleasure is related to activity rates in the medial orbitofrontal, mid insular, and the anterior cingulate areas [21]. Most of the research on the orbitofrontal cortex is concerned about sensory integration and reward value in relation to food [22]. Furthermore, these cortical areas are involved in cognitive processes like monitoring, learning, and sexual stimuli, which are memorized and produce feelings of pleasure [22].

According to creativity the dopamine receptor D2 and the polymorphism (single nucleotide polymorphism – SNP analyses) of its gene, DRD2, mediate emotional intelligence, divergent thinking, and motivation. However, other polymorphisms of genes such as of the enzyme catechol-o-methyltransferase, the dopamine transporter gene or DRD4 may also play a significant role in modulating creativity in humans [23].

According to the existing data this study focuses an evolutionary pathway on genetic selection processes in humans in relation to the evolution of creativity. From a biological point of view it is of interest to detect analogous selection pressures in humans and in our relatives, the non-human primate species. As outlined before, we think an evolutionary argument based on phylogenetic importance of creativity will justify teaching in higher education. Therefore, the same SNPs for humans, two chimpanzee species (common chimpanzee, bonobo), Sumatran orangutan, Northern white-cheeked gibbon, and two macaque species (crab eating monkeys, rhesus monkeys) were analyzed. Phylogenetically, humans diverged from chimpanzees approximately 6 Mya ago, from orangutan approximately 14 Mya ago, from gibbons approximately 18 million Mya ago, and from macaques approximately 25 Mya ago [24].

2. METHODS

Exons

We detected potential selection acting on the exons of DRD1, DRD2, DRD3, DRD4 (dopamine receptors), SLC6A3 (dopamine transporter), DBH (dopamine beta hydroxylase), and COMT (catechol-o-methyl transferase) on basis of DNA sequences from the following primate species: *Homo sapiens*, *Pan troglodytes*, *Pan paniscus*, *Pongo abelii*, *Nomascus leuconenys*, *Maccaca fascicularis* and *Maccaca mulata*.

We retrieved the DNA sequences of humans and non-human primate species from the UCSC genome browser (http://genome.ucsc.edu/). We included only coding sequences (CDS) and selection was detected later on basis of the abundance of synonymous versus non- synonymous substitutions. Using NCBI-Blast (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome) we gathered the sequences in MEGA (Molecular Evolutionary Genetics Analysis; http://www.megasoftware.net/) and aligned the sequences (codon based) applying the "*muscle alignment*" implemented in MEGA. After alignment of the sequences, we determined whether purifying, neutral or positive selection did act on the DNA sequences in all species. We carried out the z-test of selection [25], e.g., to compare the abundance of synonymous versus non- synonymous substitutions.

Introns, UTR and Upstream Variants

Additionally we analyzed 50 intronic SNPs, which are related to creativity in genetic regions on DRD1, DRD2, DRD3, DRD4, DRD5, SLC6A3, DBH and COMT, among *Homo sapiens*, *Pan troglodytes*, *Pan paniscus*, *Pongo abelii*, *Nomascus leuconenys*, *Maccaca fascicularis* and *Maccaca mulata* (detection by phyloP, implemented in the UCSC genome browser, https://genome-euro.ucsc.edu/cgi-bin/hgGateway?redirect=manual&source=genome.ucsc.edu; [26].

3. RESULTS

Exons

The pairwise comparisons of the primate sequences revealed in most cases a purifying selection on the DNA sequences. Purifying means that possible deleterious mutations had been removed by selection and the sequence is kept therefore conserved (see Table 1 – Table 8). We found no sign of any positive selection processes among any of the analyzed sequences (data not shown), *p*-values in the following tables only indicate signs of purifying selection.

Intronic and Upstream Variants in Regions of Accelerated Evolution

On DRD1 rs4532; on DRD2 rs1079596, rs1799978, rs1800498, rs6276 and rs6279; on DRD4 rs1800955 and rs936462; on SLC6A3 rs27072, rs27048, and rs27048; on DBH rs1611115, rs3025382 and rs739398, are intronic, respectively, upstream regions of accelerated evolution (Table 9). On DRD3, DRD5 and COMT none of the tested SNPs are in a region of accelerated evolution.

5. DISCUSSION

According to the description in the available data set SNPedia 50 SNPs of the dopaminergic system were found worthwhile to be analyzed in relation to creativity. From these 13 SNPs showed accelerated evolutionary processes located in introns for humans and the six non-human primate species. In contrast, the analyzed DNA sequences of exons revealed purifying selection processes. The term purifying selection expresses the elimination of deleterious alleles. The overwhelming SNPs with intronic accelerated evolution share two categories of behavioral expressions, first, psychiatric disorders, schizophrenia, antisocial behavior, bipolar disorder, neuroticism, second, substance abuse (Table 9).

Power et al. [4] showed in their work that polygenetic risk scores for schizophrenia and bipolar disorder predict creativity. Interestingly, symptoms of bipolar disorder are related to substance abuse corroborated with impulsivity behavior, which is part of recklessness of mania (maniac episodes are for example related to hyperactivity, feelings for greatness, or anger) [27].

Furthermore, the results of our comparative analyses of DRD2 genetic polymorphism revealed accelerated selection processes in two SNPs, rs6276 and rs6279. A study on healthy Chinese undergraduate students identified the same SNPs as creative potential in relation to verbal fluency [28]. This outcome is of specific interest, because it documents that humans share with non-human primates the genetic polymorphism of verbal fluency, a trait considered exclusively human. But, humans shared with macaques a common ancestor 25 Mya ago. A further DRD2 polymorphism, rs180049, from our results is worth mentioning as well. This polymorphism seems to be nearby located to the well-investigated SNP rs1800497. The latter is related to alcohol dependence [29] and associated with total creativity sores shown by Reuter et al. [30]. According to the phenotypical expression of rs1800498 a linkage to 1800497 is suggested. The remaining 10 SNPs of accelerated selection of our analyses in humans and non-human primates do allow some speculations that they are involved in causing creative potential from a phylogenetic perspective as well.

The results of our study represent some interesting and challenging insights of phylogenetic polymorphism in the order primates, however, the findings are limited. First they are limited due to our suggested interpretation and second due to our analyses. For future research genome wide associations studies have to be carried out based on the knowledge of available published works and due to the data available in genetic data banks to enable more detailed information. Notwithstanding, the authors propose regarding the SNP analyses of the recent work the following working hypothesis: creativity seems to be a trait that passed phylogenetically from non-human primates to humans. This fact should allow higher education to nurture this feature in students to increase the quality of teaching.

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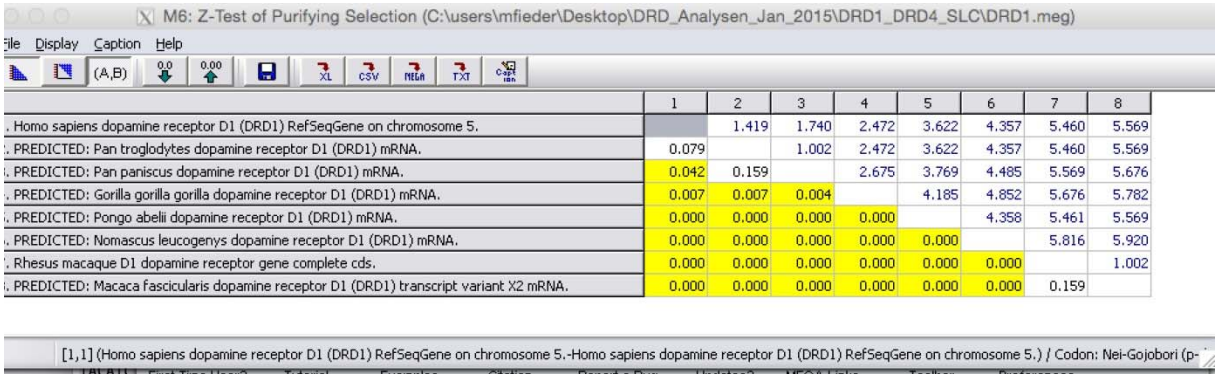
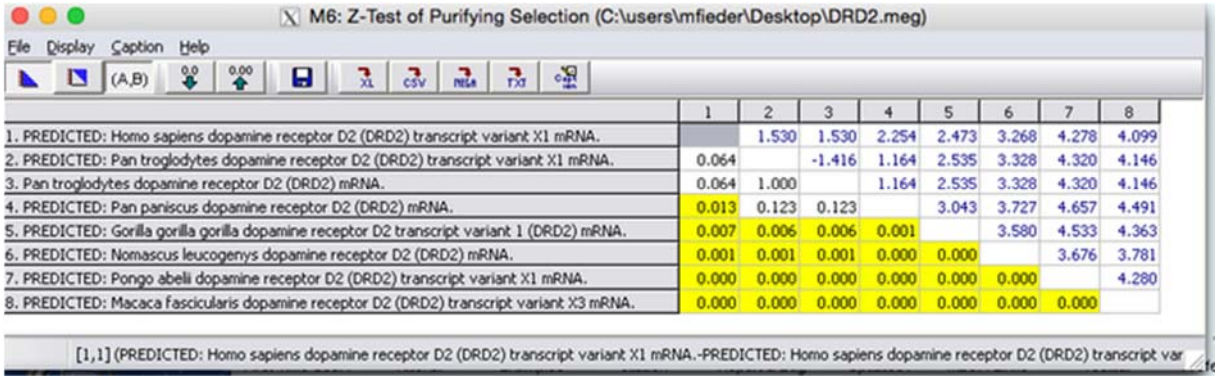


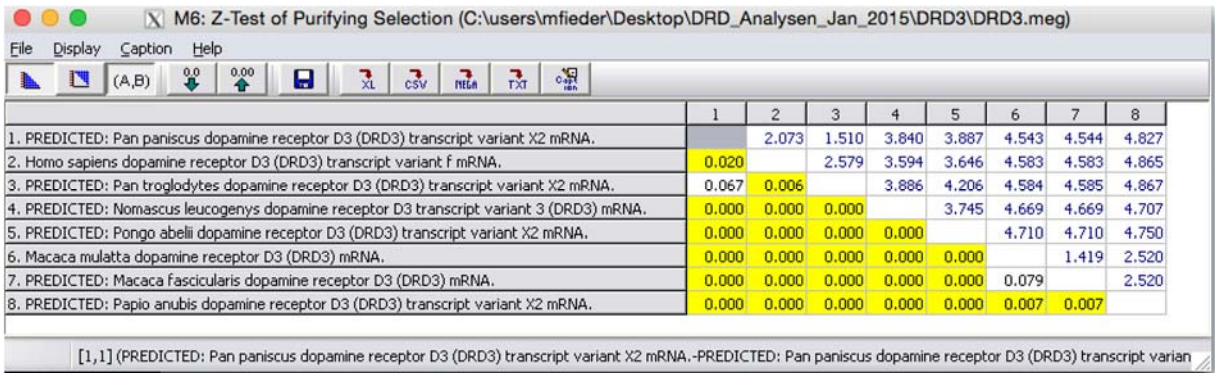
	1	2	3	4	5	6	7	8
. Homo sapiens dopamine receptor D1 (DRD1) RefSeqGene on chromosome 5.		1.419	1.740	2.472	3.622	4.357	5.460	5.569
. PREDICTED: Pan troglodytes dopamine receptor D1 (DRD1) mRNA.	0.079		1.002	2.472	3.622	4.357	5.460	5.569
. PREDICTED: Pan paniscus dopamine receptor D1 (DRD1) mRNA.	0.042	0.159		2.675	3.769	4.485	5.569	5.676
. PREDICTED: Gorilla gorilla gorilla dopamine receptor D1 (DRD1) mRNA.	0.007	0.007	0.004		4.185	4.852	5.676	5.782
. PREDICTED: Pongo abelii dopamine receptor D1 (DRD1) mRNA.	0.000	0.000	0.000	0.000		4.358	5.461	5.569
. PREDICTED: Nomascus leucogenys dopamine receptor D1 (DRD1) mRNA.	0.000	0.000	0.000	0.000	0.000		5.816	5.920
. Rhesus macaque D1 dopamine receptor gene complete cds.	0.000	0.000	0.000	0.000	0.000	0.000		1.002
. PREDICTED: Macaca fascicularis dopamine receptor D1 (DRD1) transcript variant X2 mRNA.	0.000	0.000	0.000	0.000	0.000	0.000	0.159	

Table 1. Signs of purifying selection between human and non-human primate species on the coding regions of DRD1. In the upper right section of the table the z- values of the selection coefficients are displayed and the lower left corner shows the *p*-values for the selection coefficients. Significances < 0.05 are highlighted in yellow.



	1	2	3	4	5	6	7	8
1. PREDICTED: Homo sapiens dopamine receptor D2 (DRD2) transcript variant X1 mRNA.		1.530	1.530	2.254	2.473	3.268	4.278	4.099
2. PREDICTED: Pan troglodytes dopamine receptor D2 (DRD2) transcript variant X1 mRNA.	0.064		-1.416	1.164	2.535	3.328	4.320	4.146
3. Pan troglodytes dopamine receptor D2 (DRD2) mRNA.	0.064	1.000		1.164	2.535	3.328	4.320	4.146
4. PREDICTED: Pan paniscus dopamine receptor D2 (DRD2) mRNA.	0.013	0.123	0.123		3.043	3.727	4.657	4.491
5. PREDICTED: Gorilla gorilla gorilla dopamine receptor D2 transcript variant 1 (DRD2) mRNA.	0.007	0.006	0.006	0.001		3.580	4.533	4.363
6. PREDICTED: Nomascus leucogenys dopamine receptor D2 (DRD2) mRNA.	0.001	0.001	0.001	0.000	0.000		3.676	3.781
7. PREDICTED: Pongo abelii dopamine receptor D2 (DRD2) transcript variant X1 mRNA.	0.000	0.000	0.000	0.000	0.000	0.000		4.280
8. PREDICTED: Macaca fascicularis dopamine receptor D2 (DRD2) transcript variant X3 mRNA.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

Table 2. Signs of purifying selection between human and non-human primate species on the coding regions of DRD2. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*-values for the selection coefficients. Significances < 0.05 are highlighted in yellow.



	1	2	3	4	5	6	7	8
1. PREDICTED: Pan paniscus dopamine receptor D3 (DRD3) transcript variant X2 mRNA.		2.073	1.510	3.840	3.887	4.543	4.544	4.827
2. Homo sapiens dopamine receptor D3 (DRD3) transcript variant f mRNA.	0.020		2.579	3.594	3.646	4.583	4.583	4.865
3. PREDICTED: Pan troglodytes dopamine receptor D3 (DRD3) transcript variant X2 mRNA.	0.067	0.006		3.886	4.206	4.584	4.585	4.867
4. PREDICTED: Nomascus leucogenys dopamine receptor D3 transcript variant 3 (DRD3) mRNA.	0.000	0.000	0.000		3.745	4.669	4.669	4.707
5. PREDICTED: Pongo abelii dopamine receptor D3 (DRD3) transcript variant X2 mRNA.	0.000	0.000	0.000	0.000		4.710	4.710	4.750
6. Macaca mulatta dopamine receptor D3 (DRD3) mRNA.	0.000	0.000	0.000	0.000	0.000		1.419	2.520
7. PREDICTED: Macaca fascicularis dopamine receptor D3 (DRD3) mRNA.	0.000	0.000	0.000	0.000	0.000	0.079		2.520
8. PREDICTED: Papio anubis dopamine receptor D3 (DRD3) transcript variant X2 mRNA.	0.000	0.000	0.000	0.000	0.000	0.007	0.007	

Table 3. Signs of purifying selection between the human and non-human primate species on the coding regions of DRD3. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*- values for the selection coefficients. Significances < 0.05 are highlighted in yellow.

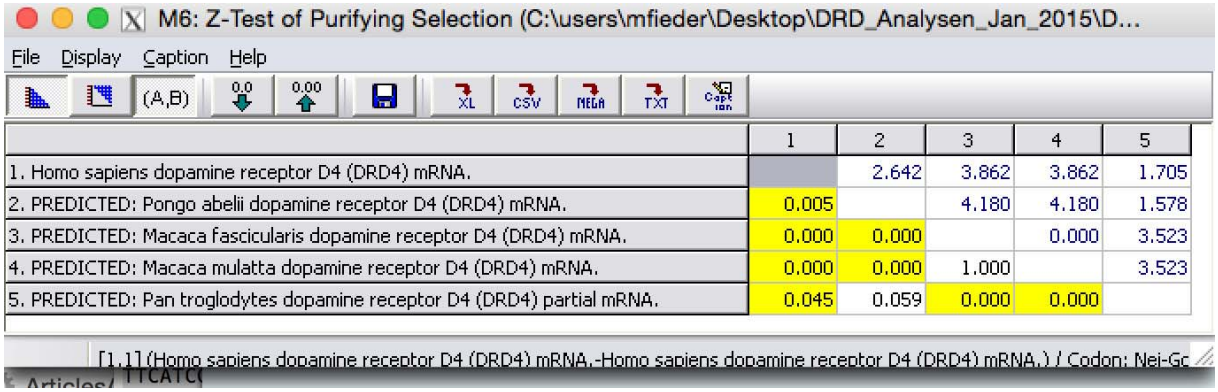


Table 4. Signs of purifying selection between human and non-human primate species on the coding regions of DRD4. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*-values for the selection coefficients. Significances < 0.05 are highlighted in yellow.

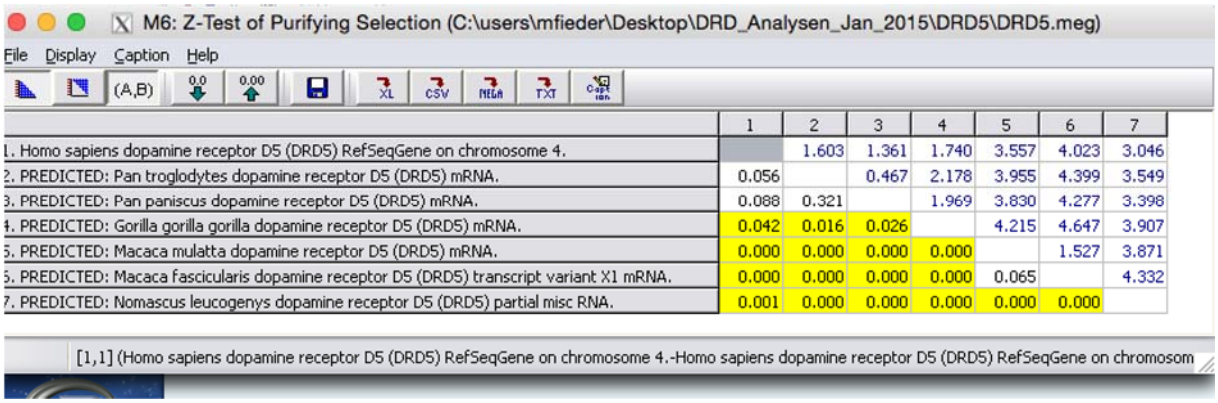


Table 5. Signs of purifying selection between human and non-human primate species on the coding regions of DRD5. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*-values for the selection coefficients. Significances < 0.05 are highlighted in yellow.

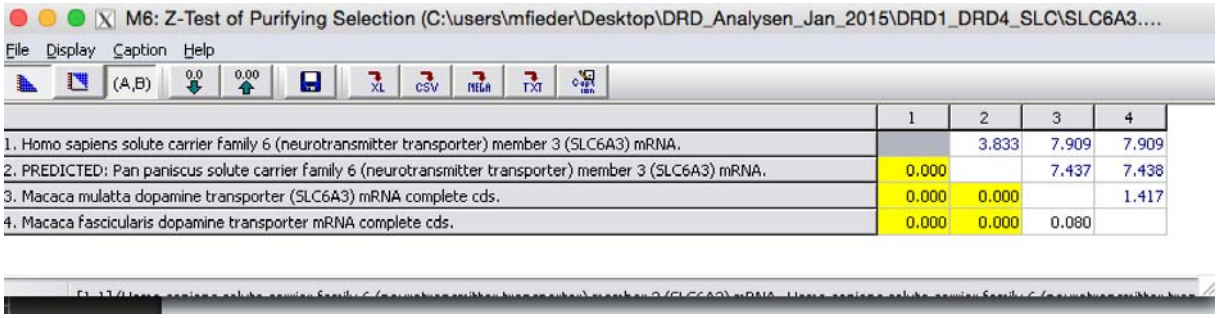
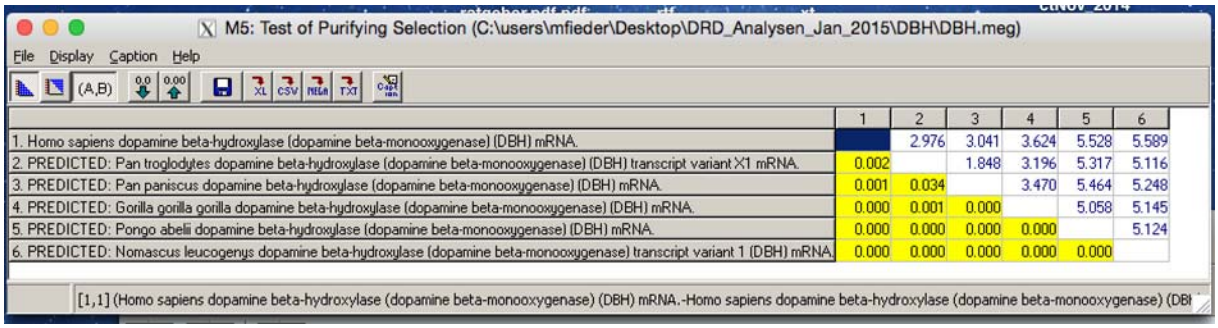
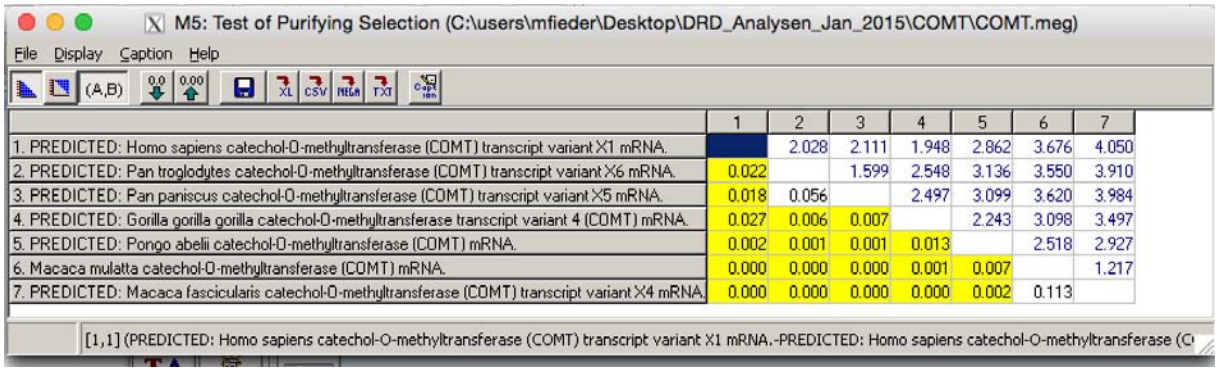


Table 6. Signs of purifying selection between human and non-human primate species on the coding regions of SLC6A3. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*- values for the selection coefficients. Significances < 0.05 are highlighted in yellow.



	1	2	3	4	5	6
1. Homo sapiens dopamine beta-hydroxylase (dopamine beta-monooxygenase) (DBH) mRNA.		2.976	3.041	3.624	5.528	5.589
2. PREDICTED: Pan troglodytes dopamine beta-hydroxylase (dopamine beta-monooxygenase) (DBH) transcript variant X1 mRNA.	0.002		1.848	3.196	5.317	5.116
3. PREDICTED: Pan paniscus dopamine beta-hydroxylase (dopamine beta-monooxygenase) (DBH) mRNA.	0.001	0.034		3.470	5.464	5.248
4. PREDICTED: Gorilla gorilla gorilla dopamine beta-hydroxylase (dopamine beta-monooxygenase) (DBH) mRNA.	0.000	0.001	0.000		5.058	5.145
5. PREDICTED: Pongo abelii dopamine beta-hydroxylase (dopamine beta-monooxygenase) (DBH) mRNA.	0.000	0.000	0.000	0.000		5.124
6. PREDICTED: Nomascus leucogenys dopamine beta-hydroxylase (dopamine beta-monooxygenase) transcript variant 1 (DBH) mRNA.	0.000	0.000	0.000	0.000	0.000	

Table 7. Signs of purifying selection between human and non-human primate species on the coding regions of DBH. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*-values for the selection coefficients. Significances < 0.05 are highlighted in yellow



	1	2	3	4	5	6	7
1. PREDICTED: Homo sapiens catechol-O-methyltransferase (COMT) transcript variant X1 mRNA.		2.028	2.111	1.948	2.862	3.676	4.050
2. PREDICTED: Pan troglodytes catechol-O-methyltransferase (COMT) transcript variant X6 mRNA.	0.022		1.599	2.548	3.136	3.550	3.910
3. PREDICTED: Pan paniscus catechol-O-methyltransferase (COMT) transcript variant X5 mRNA.	0.018	0.056		2.497	3.099	3.620	3.984
4. PREDICTED: Gorilla gorilla gorilla catechol-O-methyltransferase transcript variant 4 (COMT) mRNA.	0.027	0.006	0.007		2.243	3.098	3.497
5. PREDICTED: Pongo abelii catechol-O-methyltransferase (COMT) mRNA.	0.002	0.001	0.001	0.013		2.518	2.927
6. Macaca mulatta catechol-O-methyltransferase (COMT) mRNA.	0.000	0.000	0.000	0.001	0.007		1.217
7. PREDICTED: Macaca fascicularis catechol-O-methyltransferase (COMT) transcript variant X4 mRNA.	0.000	0.000	0.000	0.000	0.002	0.113	

Table 8. Signs of purifying selection between human and non-human primates species on the coding regions of COMT. In the upper right section of the table the z-values of the selection coefficients are displayed and the lower left corner shows the *p*- values for the selection coefficients. Significances < 0.05 are highlighted in yellow.

Table 9. A brief overview of the known phenotypic SNP expressions, which we identified with accelerated evolution.

gene	SNP	function	known phenotypical association – information comes from SNPedia
DRD1	rs4532	5_prime_UTR_variant	schizoprenia and tabacco smoking
DRD2	rs1079596	intron_variant, upstream_gene_variant	behavioral inhibition and impulsivity/sensation seeking
	rs1799978	intron_variant, upstream_gene_variant	schizophrenia, behavioral inhibition and impulsivity/ sensation seeking
	rs1800498	intron_variant	personality traits among at-risk young adults and psychiatric inpatients, addiction
	rs6276	3_prime_UTR_variant	creativity: verbal fluency, alcohol consumption
	rs6279	3_prime_UTR_variant	creativity: verbal fluency, alcohol use and problems, financial and psychological risk attitudes
DRD4	rs1800955	upstream_gene_variant	schizophrenia, anxiety and impulsivity-related traits, attention deficit hyperactivity disorder ADHD (
	rs936462	upstream_gene_variant	risk factors of heroin dependence
SLC6A3	rs27072	3_prime_UTR_variant	alcohol withdrawal, schizophrenia, AHHD, bipolar disorder, antisocial personality, emotion dysregulation and ADHD
	rs27048	intron_variant	drug abuse
DBH	rs1611115	upstream_gene_variant	ADHD, neuroticism, impulsiveness, aggression, schizophrenia
	rs3025382	intron_variant	nicotine dependence association
	rs739398	intron_variant	aggressive behavior, antisocial drug dependence