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Selection in the dopamine receptor 2 gene: New candidate SNPs for disease-related studies

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Dopamine is a major neurotransmitter in the human brain and is associated with various diseases. Schizophrenia, for example, is treated by blocking the dopamine receptors type 2. In 2009, Shaner, Miller and Mintz stated that schizophrenia was the low fitness variant of a highly variable mental trait. We therefore explore whether the dopamine receptor 2 gene (*DRD2*) underwent any selection processes. We acquired genotype data of the 1000 Genomes project (phase I), which contains 1093 individuals from 14 populations. We included only single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of over 0.05 in the analysis. This is equivalent to 151 SNPs for *DRD2*. We used two different approaches (an outlier approach and a Bayesian approach) to detect loci under selection. The combined results of both approaches yielded nine candidate SNPs under balancing selection. While directional selection strongly favours one allele over all others, balancing selection favours more than one allele. All candidates are in the intronic region of the gene and only one (rs12574471) has been mentioned in the literature. Two of our candidate SNPs are located in specific regions of the gene: rs80215768 lies within a promoter flanking region and rs74751335 lies within a transcription factor binding site. We strongly encourage research on our candidate SNPs and their possible phenotypic effects.

Selection in the dopamine receptor 2 gene: New candidate SNPs for disease-related studies.

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ABSTRACT:

Dopamine is a major neurotransmitter in the human brain and is associated with various diseases. Schizophrenia, for example, is treated by blocking the dopamine receptors type 2. In 2009, Shaner, Miller and Mintz stated that schizophrenia was the low fitness variant of a highly variable mental trait. We therefore explore whether the dopamine receptor 2 gene (*DRD2*) underwent any selection processes. We acquired genotype data of the 1000 Genomes project (phase I), which contains 1093 individuals from 14 populations. We included only single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of over 0.05 in the analysis. This is equivalent to 151 SNPs for *DRD2*. We used two different approaches (an outlier approach and a Bayesian approach) to detect loci under selection. The combined results of both approaches yielded nine candidate SNPs under balancing selection. While directional selection strongly favours one allele over all others, balancing selection favours more than one allele. All candidates are in the intronic region of the gene and only one (rs12574471) has been mentioned in the literature. Two of our candidate SNPs are located in specific regions of the gene: rs80215768 lies within a promoter flanking region and rs74751335 lies within a transcription factor binding site. We strongly encourage research on our candidate SNPs and their possible phenotypic effects.

INTRODUCTION:

The catecholamine dopamine is a neurotransmitter in the human brain. Dopaminergic neurons can be divided into four major pathways: nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular (Andén et al., 1964; Dahlstroem and Fuxe, 1964). These neurons play an important role in voluntary movement, feeding, reward and learning, as well as certain other functions. Outside of the brain, dopamine takes on a physiological role in cardiovascular functions, hormonal regulation, renal functions and other (Snyder et al., 1970; Missale et al., 1998; Sibley, 1999; Carlsson, 2001; Iversen and Iversen, 2007). Due to this involvement in many different processes and systems, dopamine is also related to a variety of diseases. Parkinson's disease, which is caused by a loss of dopaminergic innervations in the striatum, is a prominent example (Ehringer and Hornykiewicz, 1960). Additionally, the expected associations between the dopaminergic system and schizophrenia stem from the fact that various dopamine receptor 2 blockers are used as antipsychotics in treating that condition (Snyder et al., 1970; Creese et al., 1976; Seeman et al., 1976; Carlsson et al., 2001). Further relationships with dopamine dysregulation are expected in Tourette's syndrome and attention deficit hyperactivity disorder (ADHD) (Mink, 2006; Swanson et al., 2007; Gizer et al., 2009). The strong involvement of dopamine in the reward system suggests an association with drug abuse and addiction (Hyman et al., 2006; Di Chiara and Bassareo, 2007; Koob and Volkow, 2010). Many more diseases and conditions are expected to involve dopamine dysfunctions. (As reviewed by Beaulieu & Gainetdinov, 2011)

In humans, five different dopamine receptors exist. They are classified into two categories based on their structure and their pharmacological and biochemical properties. The D1-class includes the dopamine receptors 1 and 5, while the D2-class consists of the dopamine receptors 2, 3 and 4 (Andersen et al., 1990; Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff et al., 1992a; Civelli et al., 1993; Vallone et al., 2000). The focus of our study is on the dopamine receptor 2 and its gene *DRD2*. The dopamine receptor 2 gene lies on the long arm of chromosome 11 (11q23.1). It spans from 113,280,317 to 113,346,413 for a total of 66,096 base pairs (bp) (information accessed on NCBI in the GnRH37 assembly). For the gene card, see Figure 1 in Results. *DRD2* has six introns (Gingrich and Caron, 1993). Alternative splicing between intron 4 and 5 of an 87 bp exon generates two variants of the dopamine receptor 2. The

difference between D2S (short) and D2L (long) is a 29-amino-acids-long chain in the third intercellular loop of the protein (Giros et al., 1989; Monsma et al., 1989). While the short form (D2S) is mainly expressed at the presynapse, the long form (D2L) is expressed postsynaptically (Usiello et al., 2000; De Mei et al., 2009). The D2S are mainly autoreceptors, i.e. they reduce the expression of dopamine when activated. This leads to an important negative feedback mechanism (Wolf and Roth, 1990; Missale et al., 1998; Sibley, 1999). (Again, as reviewed by Beaulieu & Gainetdinov, 2011)

Among the many single nucleotide polymorphisms (SNPs) of *DRD2*, one prominent example is rs6277, also known as C957T. It has been associated with schizophrenia in Han Chinese in Taiwan (Glatt et al., 2009), in Russians (Monakhov et al. 2008) and in Bulgarians (Betcheva et al. 2009). Together with the -141C allele, the 957T allele is associated with the diagnosis of anorexia nervosa (Bergen et al., 2005). A meta-analysis showed that the Ser311Cys polymorphism (rs1801028) in *DRD2* is a risk factor for schizophrenia. The heterozygotes (Ser/Cys) and the homozygotes for Cys were both at elevated risk for schizophrenia when compared to the Ser/Ser genotypes (Glatt and Jönsson, 2006). In a study with alcoholic patients and controls, the A allele of rs1076560 was more frequent in alcoholic patients (Sasabe et al., 2007). In 2012, Mileva-Seitz et al. conducted a study with Caucasian mothers and their infants. They taped mother-infant behaviour and genotyped various SNPs of *DRD2* and also *DRD1*. Rs1799732 and the previously mentioned rs6277 were both associated with direct vocalization of the mother towards the infant.

The body of literature on SNPs and their possible effects is growing rapidly. Considering the influences those SNPs could have on human behaviour, and bearing in mind the different ecological habitats of *Homo sapiens*, we aimed to explore if *DRD2* underwent any selection processes. In 2009 an interesting proposal by Shaner, Miller and Mintz stated that schizophrenia was the low fitness variant of a highly variable mental trait. Because of the connection between dopamine receptor 2 and schizophrenia, as stated above, we focused our analysis on *DRD2*.

To reduce false-positives, we used two selection detection algorithms to explore *DRD2*. This is an exploratory ("hypothesis-free") approach in which we want to find candidate SNPs that were under selection. The data basis of our analysis are the 1000 Genomes Project samples.

MATERIAL AND METHODS:

We acquired data from the 1000 Genomes Project (phase I) through SPSmart engine v5.1.1 (http://spsmart.cesga.es/engines.php; Amigo et al., 2008), using the search term "DRD2". We included all single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) greater than 0.05. Over the span of the whole *DRD2* gene (113,280,317 – 113,346,413 in the GnRH37.p13 primary assembly; gene card shown in Results, Figure 1), this amounts to 151 SNPs. In total we included the following populations in our analysis.

Superpopulation (Code)	**Population Code**	**Population**	**Number of Individuals**
Africa (AFR)	ASW	African ancestry in Southwest USA	61
	LWK	Luhya in Webuye, Kenya	97
	YRI	Yoruba in Ibadan, Nigeria	88
Europe (EUR)	CEU	Utah residents with Northern and Western European ancestry	87
	FIN	Finnish from Finland	93
	GBR	British from England and Scotland	88
	IBS	Iberian populations in Spain	14
	TSI	Toscani in Italy	98
East Asia (ASN)	CHB	Han Chinese in Bejing, China	97
	CHS	Han Chinese South	100
	JPT	Japanese in Tokyo, Japan	89
America (AMR)	CLM	Colombians from Medellin, Colombia	66
	MXL	Mexican ancestry from Los Angeles USA	60
	PUR	Puerto Ricans from Puerto Rico	55
		All populations =	1093

Table 1. Populations of the 1000 Genomes Project.

The data was converted by hand into the CONVERT format. All further format conversions were performed by PGD Spider 2.0.5.2 (Lischer and Excoffier, 2012).

Two different programs were used to detect selection. Both use F_{ST} approaches to detect outliers. The program LOSITAN calculates FDIST, which uses F_{ST} and the expected heterozygosity. It assumes an island model of migration with neutral markers. An expected distribution of Wright's inbreeding coefficient is calculated and then outliers are identified. A neutral mean F_{ST} was computed by the program before the 50,000 simulations were performed. The infinite alleles model was used. To avoid false positive detection we set the significance level to $p < 0.01$ ($P(\text{Simulation } F_{ST} < \text{sample } F_{ST})$). (Antao et al., 2008)

BayeScan is a Bayesian statistics program. Basically it calculates two simulations for every loci: one in which it assumes the locus is under selection and the other one in which this assumption is dropped. It splits the F_{ST} coefficient into two parts. The alpha value is a locus-specific component shared by all populations. The beta value is a population-specific component shared by all loci. This is achieved via logistic regression and provides insight into selection. The alpha value serves as an indicator for selection. Significant positive values of alpha indicate directional selection, whereas significant negative values indicate balancing selection. The posterior probabilities are estimated using a reversible-jump Markov Chain Monte Carlo (MCMC) approach. The posterior probabilities are gained by counting how many times alpha is included in the model. Before the Markov chains are computed, we calculate 20 pilot runs with 5000 iterations each. The initial burn-in is set to 50,000 steps and the chains are run with 5000 iterations and a thinning interval of 10. The program output consists of a posterior probability, the logarithm (base 10) of the posterior odds and a q value. These three values are all for the model with selection. Furthermore, the alpha value is reported and an F_{ST} coefficient average of all population per locus. In BayeScan the threshold of a posterior P of > 0.99 and a log10(PO) of 2 or higher is used. This threshold is labelled as "Decisive" by BayeScan (see the program manual at http://cmpg.unibe.ch/software/BayeScan/files/BayeScan2.1_manual.pdf). (Foll and Gaggiotti, 2008)

To compute linkage disequilibrium (LD) of the SNPs, we used the R "genetics package" (http://cran.r-project.org/web/packages/genetics/genetics.pdf; Warnes et al., 2013). We used D'

as a measurement for LD. In most populations one or more SNPs had to be excluded to successfully run the computation. The population IBS was excluded entirely from this computation. IBS is a very small population (n = 14), and 30 SNPs caused the computation to fail. For a detailed view on all excluded SNPs see Table S1 in the supplementary material.

We accessed information on the gene via NCBI (http://www.ncbi.nlm.nih.gov/) and on the specific SNPs via Ensembl (http://www.ensembl.org/).

127 RESULTS:

128 The combined results of LOSITAN and BayeScan yielded nine candidate SNPs under balancing
129 selection:

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Locus	Major Allele (Frequency)	Minor Allele (Frequency)	F_{ST} (Lositan)	F_{ST} (BayeScan)	Location
rs60599314	C (0.871)	T (0.129)	0.0110	0.0272	113,306,431 (Intronic region)
rs79549222	T (0.87)	G (0.13)	0.0106	0.0260	113,310,340 (Intronic region)
rs12574471	C (0.891)	T (0.109)	0.0172	0.0364	113,316,236 (Intronic region)
rs80215768	G (0.925)	A (0.075)	0.0304	0.0328	113,318,880 (Intronic region)
rs76581995	C (0.925)	A (0.075)	0.0304	0.0328	113,319,835 (Intronic region)
rs80014933	T (0.923)	C (0.077)	0.0304	0.0332	113,328,135 (Intronic region)
rs74751335	G (0.915)	C (0.085)	0.0266	0.0322	113,328,810 (Intronic region)
rs77264605	A (0.915)	G (0.085)	0.0266	0.0327	113,328,913 (Intronic region)
rs76499333	G (0.925)	A (0.075)	0.0299	0.0327	113,329,449 (Intronic region)

131 Table 2. The dopamine receptor 2 gene's nine candidate SNPs for balancing selection.

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For a detailed view on the results of LOSITAN and BayeScan for all SNPs, see Table S2 in the supplementary material. In Figure 1 a gene view of *DRD2* with labels for the candidate SNPs is provided.

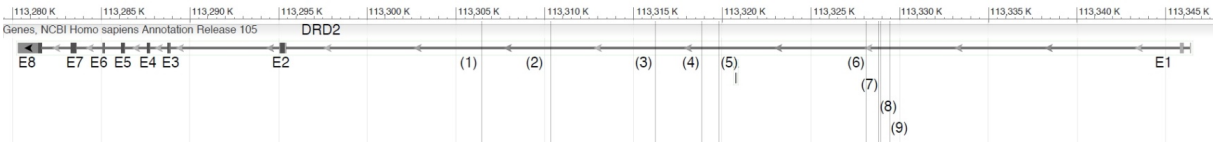

Figure 1. Location of candidate SNPs under balancing selection in *DRD2*.
E1-8 are exons 1 to 8. (1): rs60599314, (2): rs79549222, (3): rs12574471, (4): rs80215768, (5): rs76581995, (6): rs80014933, (7): rs74751335, (8): rs77264605, (9): rs76499333.

All nine SNPs are intron variants (Figure 1). Only rs12574471 (3) is mentioned in the literature because it is near a supposed recombination hotspot (Glatt et al, 2009). rs80215768 (4) lies within a promoter flanking region; rs74751335 (7) lies within a transcription factor binding site. However, we found no known associations for those two SNPs.

The F_{ST} values of these nine loci indicate an overall low genetic differentiation, as well as a low differentiation between populations (Table 2). This is in accordance with balancing selection acting on the gene. The differences in F_{ST} values stem from different algorithms used by the programs.

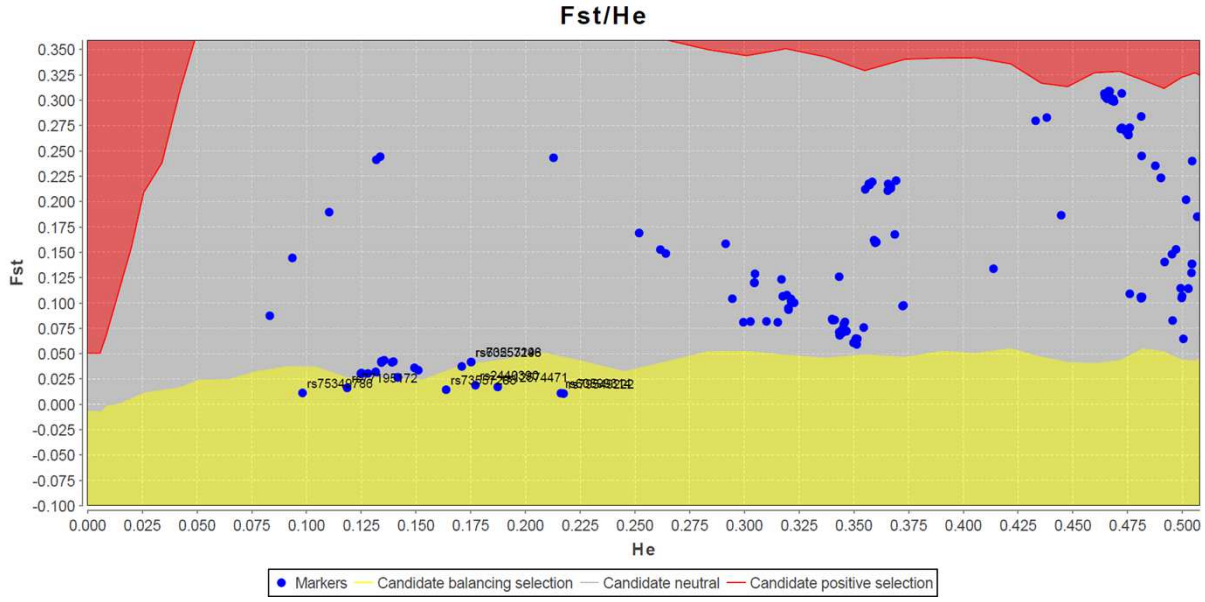

Figure 2. LOSITAN graphical output. Yellow area = candidate loci for balancing selection. Grey Area = neutral. Red area = candidate loci for positive selection.

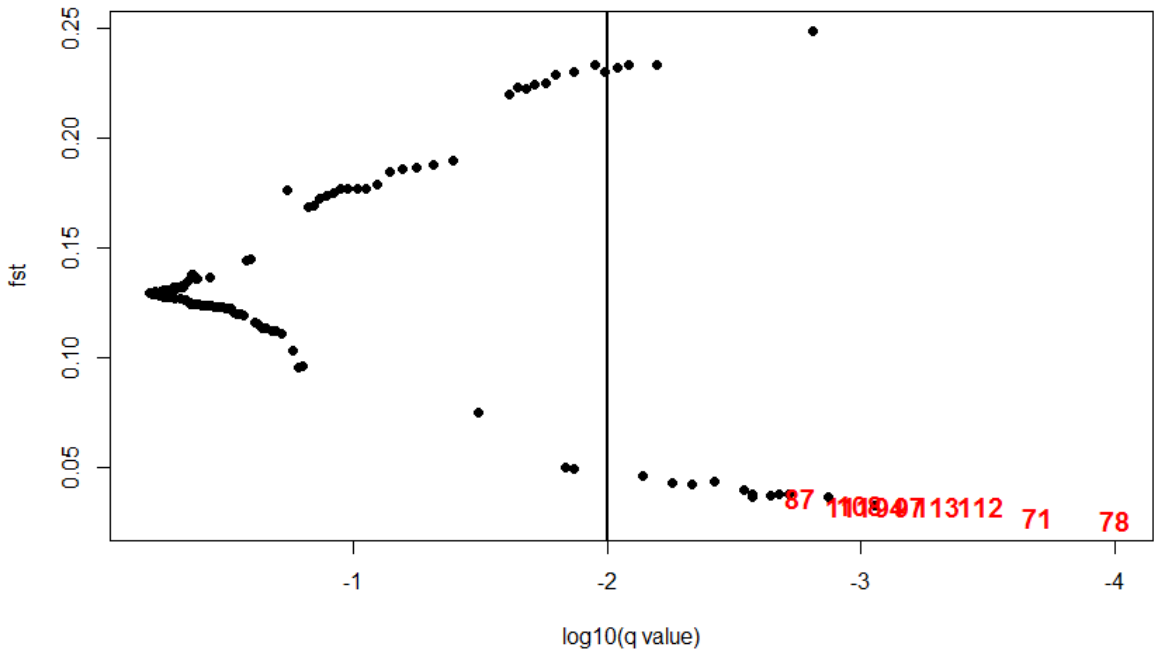

Figure 3. Graphical output of BayeScan. The red numbers represent the overlapping SNPs with LOSITAN. 71 = rs60599314, 78 = rs79549222, 87 = rs12574471, 94 = rs80215768, 97 = rs76581995, 108 = rs80014933, 111 = rs74751335, 112 = rs77264605, 113 = rs76499333. For the exact values see Table S2 in the supplementary material.

The Linkage Disequilibrium measurement D' was used. The heat maps for all nine populations are shown in the supplementary material (Figure S1 – S13). The relative position of the marked SNPs change because different populations had different SNPs excluded (see Table S1 for the list).

DISCUSSION:

We found nine SNPs to be candidates for balancing selection and none for directional selection. Checking those SNPs with Genome Browser reveals that they are all intronic region variants. rs80215768 (4) lies within a promoter flanking region and rs74751335 (7) lies within a transcription factor binding site (TFBS). There have been many studies on the possible effects of mutations in such regions (Hayashi, Watanabe and Kawajiri, 1991; and In et al. 1997; or for a more general review on the topic, Jaenish & Bird, 2003). We strongly encourage further analysis of those two SNPs in order to analyse their possible effects. Nonetheless, the SNPs show low F_{ST} values, which is congruent with the finding of balancing selection. Sewall Wright's guidelines for interpreting F_{ST} values suggest little genetic differentiation in our populations (as cited by Jobling, 2013; Chapter 5, Box 5.2). As silent mutations in *DRD2* are known to alter the mRNA stability and even the synthesis of the receptor itself (Duan et al., 2003), we should be eager to explore the possible effects of these SNPs.

Additionally, the levels of the linkage disequilibrium measurement D' are typical for the respective populations: African populations show a dispersed pattern and no clear LD blocks (Figure S1, S9, and S13). While the LD blocks are visible in American populations (Figure S5, S10 and S11), they are not as clear as in Asian (Figure S3, S4 and S8) or European populations (Figure S2, S6, S7 and S12). Looking up the SNPs that are in high D' (> 0.8) with our nine candidate loci revealed no new information as to the nature of those loci.

All of our SNPs have a MAF > 0.05 and there are some individuals (0.8 – 2.3% per SNP, over all populations) that are homozygote for the minor allele. The finding of balancing selection suggests that in our sample the minor alleles bear some fitness disadvantage. Fitness is altered if survival or reproduction of an organism is affected. This raises the possibility of a connection between our candidate SNPs and diseases or malfunctions of dopamine receptor 2. In the list of diseases associated with dopamine (see Introduction) the most striking example is schizophrenia because dopamine receptor 2 blockers can successfully treat patients. Leaving the biochemical field, we can also find connections with diseases on a molecular level. Rs6277 is associated with schizophrenia in Han Chinese in Taiwan (Glatt et al., 2009), in Russians (Monakhov et al. 2008) and in Bulgarians (Betcheva et al. 2009). Rs1801028 was also described as a risk factor for schizophrenia (Glatt and Jönsson, 2006). Bergen et al. (2005) found an association between the

alleles -141C and 957T and the diagnosis of anorexia nervosa. The A allele of rs1076560 was more frequent in alcoholic patients when compared with a control group (Sasabe et al., 2007). In a meta-analysis, Le Foll et al. (2009) concluded that there are associations between variants of *DRD2* and alcohol dependency.

The question is whether these conditions could potentially affect fitness. Bassett et al. (1996) showed that reproductive fitness is reduced in groups of familial schizophrenia, which suggests a selection process. Puzzlingly enough, they also found some evidence for an increased fitness of a small subsample of sisters. Shaner, Miller and Mintz in 2009 proposed that schizophrenia is the low-fitness trait of a highly variable mental trait. They argue that the persistence of the illness at about 1% globally is too high for new mutations. Balancing selection would fit this hypothesis very well and our candidate SNPs could be viable indicators for this. Interestingly, rs6277 and rs1801028, which are both associated with schizophrenia (Glatt et al., 2009; Monakhov et al. 2008; Betcheva et al. 2009; Glatt and Jönsson, 2006), are candidates for neutral loci in our study. Note that also the other SNPs that are associated with alcohol dependency, anorexia nervosa or even the behaviour of mothers with their infants, are all candidates for neutral loci. This method does not allow us to make direct inferences about a phenotype (e.g. schizophrenia). We can only make assumptions about the phenotype based on our genotype data. This study is a potential precursor to future studies on the subject.

Lastly, what also should pique our interest is the fact that we only found candidates for balancing selection. We extended our analysis to the other 4 dopamine receptors and again only found candidates for balancing selection and none for directional selection (data not shown). Note that this applies only to SNPs. There has been evidence for directional selection in *DRD4*, by analysing a tandem repeat in the coding region (Ding et al. 2001). Recently, *DRD1* has been analysed as one of ten neurochemical genes that are responsible for the Social-Decision Making System (O'Connell & Hofmann, 2012). The study finds that the system underwent very little change during evolution. The authors wanted to include *DRD2* but too little data for different species were available. The fact that we find only balancing selection and no directional selection acting upon *DRD2* hints that it is a conserved region within the human genome.

To untangle the possible effects of our SNPs we propose a study in which our candidate SNPs are investigated in schizophrenic and non-schizophrenic persons. A simple comparison of the

SNPs and the different haplotypes between the two groups should efficiently assess our findings. If this proposed study finds differences in those two groups, the mechanisms of those SNPs and their possible haplotypes must be investigated.

CONCLUSION:

We found nine candidates for balancing selection on *DRD2* but no evidence for directional selection. Some of the nine candidate SNPs under selection are potentially associated with various diseases. These SNPs could be important as biomarkers due to their very low F_{ST} values: the genetic differentiation of one population compared with the whole sample is very small. While all candidate SNPs may be worth exploring, we definitely recommend using rs80215768 and rs74751335 in further studies on *DRD2* because rs80215768 is within a promoter flanking region and rs7451335 lies in a transcription factor binding site. The dopaminergic system, and thus also its genes, seem to play a very basal role in animals. Accordingly, our finding of balancing selection is in line with our expectations, i.e. a finding of directional selection within a current sample of humans would have indeed been very striking.

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