Oxytocin and Vasopressin Receptor variants as a window onto the evolution of human prosociality

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ABSTRACT

Modern humans' lifestyle strongly depends on complex social skills like empathy, tolerance and cooperation. Variation in the oxytocin receptor (*OXTR*) and the arginine-vasopressin receptors (*AVPR1A*, *AVPR1B* genes) has been widely associated with diverse facets of social cognition, but the extent to which these variants may have contributed to the evolution of human prosociality remains to be elucidated. In this study, we compared the *OXTR*, *AVPR1A* and *AVPR1B* DNA sequences of modern humans to those of our closest extinct and extant relatives, and then clustered the variants we identified based on their distribution in the species studied. This clustering, along with the functional importance retrieved for each variant and their frequency in different modern-human populations, is then used to determine if any of the *OXTR*, *AVPR1A* and *AVPR1B*-variants might have had an impact at different evolutionary stages. We report a total of 29 SNPs, associated with phenotypic effects ranging from clearly pro-social to mixed or antisocial. Regarding modern human-specific alleles that could correlate with a shift towards prosociality in modern-humans, we highlight one allele in *AVPR1A* (rs11174811), found at high frequency and linked to prosocial phenotypes in modern humans, while the ancestral allele is associated with antisocial phenotypes. We also report three sites of putatively convergent changes between modern humans and bonobos (rs237897(A), rs2228485(G) and rs1042615(A)), and note the absence of such a convergent pattern between modern humans and chimpanzees. Finally, we observe the high concentration of 'modern human specific' alleles in vasopressin receptors not paralleled in the oxytocin receptor.

1 Introduction

Oxytocin (OXT) and vasopressin (AVP) are important neurotransmitters that function through their respective receptors to regulate a diverse set of biological processes, such as pregnancy and uterine contractions, milk-ejection, copulation and orgasm, attachment between mothers and their young, bond formation, suppression of stress, thermoregulation, olfactory processing, eye-contact and recognition of familiar individuals[1]. OXT and AVP are closely related structurally and evolutionarily: they have been argued to be the product of a local duplication event that took place before the origin of vertebrates[2], and they only differ in two (of the nine) amino acids, although they display differences at a functional level[1]. Each binds to their respective receptor(s) (*OXTR* in the case of oxytocin, and *AVPR1A*, *AVPR1B*, and *AVPR2* in the case of vasopressin), but their molecular similarities allow for crosstalk in the brain and peripheral organs[3].

Variation in the genes that code for OXT and AVP receptors (*OXTR* and mainly *AVPR1A* and *AVPR1B*) have long been associated with different social behaviors[4]. Single Nucleotide Polymorphisms (SNPs) in these genes in modern humans have been claimed to be implicated in altruism, face recognition, stress levels and empathy, but also in sociocognitive disorders, such as Autism Spectrum Disorders (ASD), bipolar disorder, schizophrenia or depression[1,5]. Due to the paucity of studies on social effects of *AVPR2*, we did not include this receptor in the present study.

The role oxytocin and vasopressin play in social cognition makes them prominent candidates to test for possible social behavioral differences between hominid species (extinct and extant). In this study we examine the extent to which variation in the OXT and AVP receptors correlate with social characteristics that have already been put forth in the literature to characterize the prosocial profile of each of the species studied here (modern humans, archaic humans such as Neanderthals and Denisovans, bonobos and chimpanzees). 'Prosociality' is a broad term that encompasses intraspecies empathy, social tolerance, cooperation and altruism. While our closest living relatives, the chimpanzees (*Pan Troglodytes*) and the bonobos (*Pan Paniscus*), live in highly organized social groups as well, present-day humans' social networks are larger and denser, powered by a complex social cognitive machinery[6]. Modern humans are characterized by great intrasocial compassion, are motivated by concern

about the welfare of out-group individuals, and display a clear tendency to act in concert, to the extent that *Homo Sapiens* has been labeled as 'ultra-social'[7]. This trait is of special relevance, as it has been argued to underlie other singular traits of humans, such as their enhanced verbal communicative skills[6–10].

The sequencing of two Neanderthal genomes from Altai (Siberia)[11] and Vindija (Croatia)[12] and a Denisovan from Altai[13] has made available genomic data to provide new insights into the discussion of the evolution of social cognition, complementing the archaeological evidence. Today, various hypotheses[6,10,14,15] still offer different explanations and timelines for the emergence of prosociality, ranging from the *Pan-Homo* split to later stages of human evolution, such as the split between Neanderthals and Denisovans on the one hand, and Modern Humans on the other. The critical effect of OXT and AVP on pair-bonding has led some of the authors of the aforementioned theories, most prominently,[14], to ascribe to them a key role in the emergence of human social behavior, while others have challenged the centrality of OXT and AVP in this shift in favor of other hormones, such as β-endorphines and dopamine[10,16]. By examining the evolutionary variation in human OXT and AVP receptors, we aim to shed light onto the timing of the transition towards the current status of human prosociality, as well as determine more clearly the specific role that OXT and AVP could have played in this regard.

As of now, none of the studies searching for fixed changes between modern and archaic humans (Neanderthals and Denisovans) have identified changes on the genes coding for the OXT and AVP ligands and receptors[11,17]. The only study[17] systematically exploring non-synonymous changes at high frequency in modern humans for which archaic humans carry the ancestral state found that *AVPR1B* is in the top 5% of the genes enriched for high frequency-changes in modern humans (controlling for gene length).

For this reason, in this study we investigated the variants that differ in modern and archaic humans on the *OXTR*, *AVPR1A* and *AVPR1B* genes, focusing on those that are polymorphic in modern humans and that have been associated with specific behavioral correlates in the literature, using also allele-frequency data from modern humans of different ethnic backgrounds. In order to infer the ancestral state (allele) of these sites we used primate species' sequences (rhesus macaque, chimpanzee, bonobo). We also took into account variation data (Single Nucleotide Variants: SNVs) from multiple chimpanzee and bonobo individuals. We identify various changes in the analyzed genes which we clustered in different evolutionary stages, based on their distribution (presence or absence) in the different species/populations studied (e.g. Homo-specific, modern human-specific, Altai Neanderthal-specific). These changes have been reported in the literature to affect gene expression, brain regions such as the mesolimbic reward system, and behavioral phenotypes. A fair amount of those polymorphic sites also confer risk of sociocognitive disorders, like Autism Spectrum Disorder (ASD). Finally, we discuss how the information we have gathered bears on several hypotheses concerning the evolution of human prosociality, including the neurochemical hypothesis[10], the social-brain hypothesis[6] and the self-domestication hypothesis[14,15].

2 Results

The DNA sequence-alignment we performed gave rise to a list of SNPs that we ordered in clusters (shown in Tables 1-2), based on their distribution in the sequences studied, with the major distinction being SNPs present only in modern humans (MHS: modern human-specific) *vs.* SNPs shared between modern humans and one or more archaics, and those distiguishing *Homo* from *Pan*. In this section we present the SNPs we identified, along with their potential functional relevance, based on data mining as well as our independent analysis (SNAP2 test). We discuss the results following their distribution pattern: from total overlap (alleles found in all the species considered) to no overlap at all (e.g., alleles found exclusively in modern populations, or MHS), and summarize the key information in Table 1 (for the oxytocin receptor) and Table 2 and 3 (for vasopressin receptors). Figures 1-2 provide graphic summaries of the main results. Frequencies of the relevant alleles in modern human populations retrieved from the sources consulted (see Methods) are provided in Supplementary Tables 1-2. A series of archaic human-specific variants were also identified and are reported in Supplementary table 3. Just one of them (rs199856198, G/A) was found to be an extremely rare allele in modern humans ($<$0.002). Rs199856198 is a missense variant in exon four of *OXTR* that changes Threonine for Methionine at the 360th position. While its effects have not been investigated, the SNAP2 test we performed gave a predicted 63% for a possible effect on the phenotype.

Only four alleles discussed here are not shared by the three non-human primates we used: rs237897(A) and rs2228485(G) are shared between modern humans and only bonobos; and rs11131149 (A) is found also in rhesus macaques (*Macaca mulatta*), but not in chimpanzees or bonobos.

2.1 Oxytocin receptor

The intronic variants rs11131149(A), rs59190448(G) and rs13316193(C), the 3'-UTR variant rs9872310(G) and the missense SNP rs4686302(T) are found in both present-day populations and the three ancient human sequences used in this study. Rs11131149(A), already attested in macaques, has been reported to have the reverse effect of the G allele, which is found in chimpanzees and bonobos and correlates with higher social performance (empathy, joint attention, cooperation and self-recognition) in 18 month-children[18]. Interaction between the G allele and maternal cognitive sensitivity accounted for a 26% of

variability in a Theory of Mind scale in 4.5 year old-children[18]. Rs11131149(G) is also part of a haplotype related to depressive temperament[19].

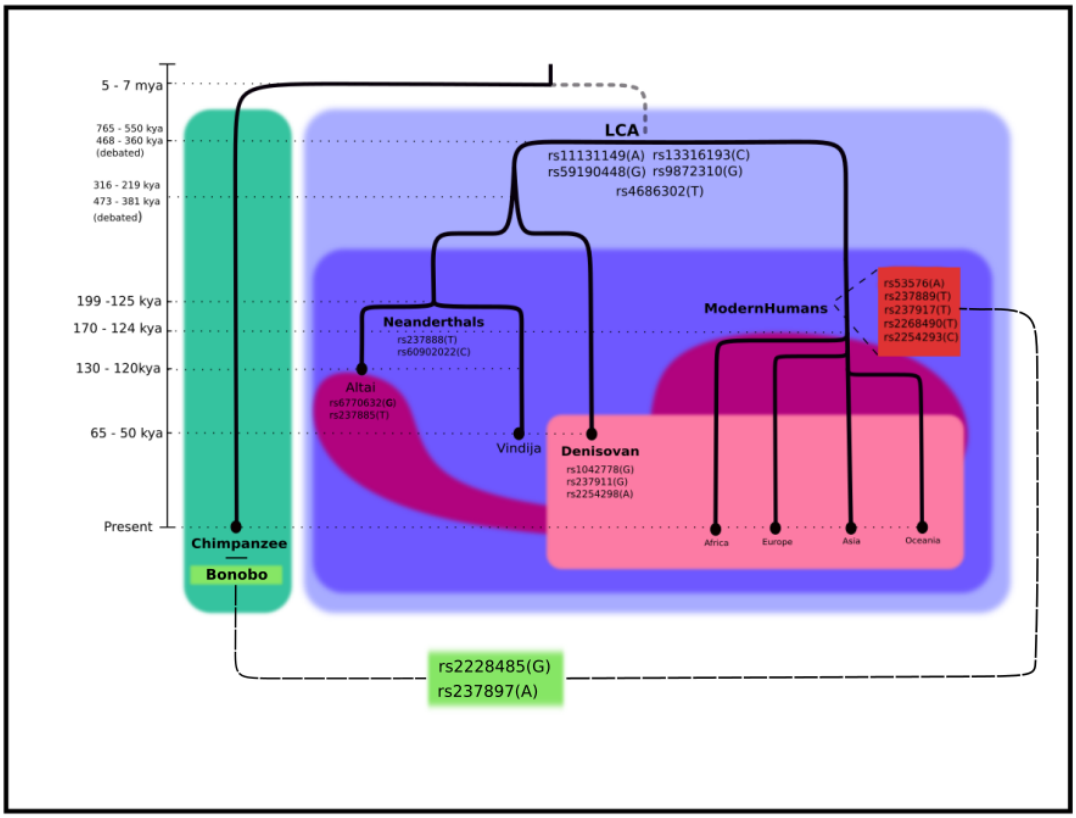

Figure 1. Evolutionary distribution of *OXTR* alleles. The alleles displayed are the non-ancestral ones. LCA = Last Common Ancestor.

Rs59190448(G) has been argued to show signs of positive selection in present-day humans[20]. The only known endophenotype associated with it is increased risk of anxiety, stress and depression in early life[21]. Rs13316193(C) has been related to empathy[22] and high cooperation and comforting skills[23], but also to late onset of Obsessive Compulsive Disorder[24], poorer social skills[25] and significant association with Attention Deficit/Hyperactivity Disorder (ADHD) on the Social Communication Questionnaire[26]; rs13316193(T) is part of a haplotype linked to ASD[27], depressive mood[19], and poorer empathic communication in relationships[28]. The T allele also affects *OXTR* total gene expression in the brain[29]. Rs9872310(G) has been implicated in altruism and ASD in different studies[27,30], but its specific functionality has not been investigated further. The rs4686302(T) allele benefits perspective taking[22] and social connectedness (in men)[31] compared to the C allele, while ADHD T-carriers performed significantly worse on the face emotion recognition task than C-carriers[31].

OXTR alleles rs237888(T) and rs60902022(C), both intronic, are found in both (Altai and Vindija) Neanderthal sequences but are absent in the Denisovan sequence. The ancestral allele rs237888(C) has been associated with daily life-skills score in the Vineland Adaptive Behavior Scales (VABS) test in ASD patients, as well as with IQ measurements[27], and the T allele has been linked to greater impairment in ASD[32]. Rs237888 is part of a haplotype related to altruism in the Dictator Game[30](an experimental economics paradigm where participants have to assign amounts of money to different individuals) and it has been also been associated with DNA methylation of specific CpG sites (cg25140571 and cg00247334) that are linked to abuse and psychiatric symptoms[33]. Rs60902022(C) has been claimed to affect gene expression and transcription factor binding by linkage disequilibrium (LD) with other *OXTR* variants[34].

In addition to these SNPs, we identified in the Altai Neanderthal *OXTR* sequence two present-day human alleles not found

in the Vindija and Denisova sequences: rs6770632(C) and rs237885(T). The 3'UTR rs6770632(G) has been associated with VABS scores[27] and persistent, extreme aggression, with the C and T alleles affecting male and female children, respectively[35]. rs237885(T) has been associated with callous/unemotional traits[35], ASD[36], schizophrenia diagnosis[37] and higher risk of aggression[38], while the G allele is linked to altruistic allocations in the Dictator Game[30].

Modern human alleles found in the Denisovan individual but not in Altai or Vindija Neanderthals are rs1042778(G), rs2254298(A) and rs237911(G). The T allele of rs1042778 has been associated with lower levels of OXT in plasma, diminished parental care (parent-child gaze and touch)[39] and panic/aggressive behaviors[40], while the G allele has been linked to ASD[27,40,41] and to aggression in males[35]. However, this latter association is at odds with other findings concerning the G allele reporting a significant correlation with prosocial fund allocations in the Dictator Game setting[30] (although[42] failed to replicate the result) and higher scores in altruistic and comforting behaviors[23]. According to[43], T-allele carriers are likely to recover from the effects of low maternal emotional warmth and acceptance, whereas G-carriers do not show such a pattern. But based on another study[44], it was G allele-carriers who experienced gains in daily positive emotions from loving-kindness training, whereas individuals with the T allele did not. Additionally, it has been suggested that rs1042778(G) influences *OXTR* transcription and translation processes, as well as *OXTR* gene expression in the amygdala[29,30].

Rs2254298(A) and rs237911(A) are overtransmitted in ASD patients[36,45], a result confirmed in a meta-analysis that included eleven cohorts[46]. Such effects seem to depend on ethnicity, as[45] and[36] used Chinese and Japanese samples, while a study using a Caucasian sample found rs2254298(G) to be the variant associated with ASD[27,47]. rs2254298(G) has been associated with lower communication scores in romantic relationships[28], variation in empathy scores[22], methylation at cg11589699 (a site linked to depression and anxiety level increase)[48], less sensitive parenting and lower plasma OXT levels[39], but also with higher values of positive affect and lower scores in depressive temperament in a Japanese sample[19].

Rs2254298(A) carriers performed better in self-reported empathy[37] and empathy for pain in particular[49], parenting[50] and in attachment security tests (in a non-Caucasian children sample)[51], while A-ADHD-carriers displayed fewer social deficits[26]. On the contrary, A-ASD-carriers presented more social deficits[26] and lower serum OXT-levels[52]. This allele has also been related to prosopagnosia[53], high levels of physical aggression and hostility[54] and low emotion recognition and resilience skills[55]. G-carriers showed higher levels of retrospective self-report of inhibition and adult separation anxiety[56] and, compared to A-carriers, are more vulnerable to antisocial behavior if they experience maltreatment[57]. This SNP also has interesting anatomical associations: the A allele was associated with larger amygdalar volume in healthy Asian adults[58,59], a phenotype typically identified in the early stages of autism[58], and which correlated with heightened amygdala response during two functional magnetic resonance imaging (fMRI) tasks that involved viewing socially-relevant face stimuli[59]. However, this association was not replicated though in a healthy Caucasian sample[60]. Gender might be playing a role in these associations, since A-female carriers showed smaller left amygdala volume, while it was G-male-carriers that showed smaller left amygdala, which was also negatively associated with attitudinal trust[61].

Finally, the intronic alleles rs2268490(T), rs2268493(C), rs237889(T), rs237917(T), and rs53576(A) were only present in modern human populations. In addition, the intronic rs237897(A) and the synonymous variant rs2228485(G) are only attested in modern human populations and in bonobos, and are thus putative instances of convergent evolution.

The archaic rs2268490(C) allele positively affects the amount of funds altruistically given in the Dictator Game setting[30] and might provoke vocal alterations under stress. Carriers of the MHS C allele displayed more stress-related vocal symptoms (dysphonia, muscle tension, frequency changes) and higher cortisol levels[62]. The MHS allele rs2258493(T) has been linked to ASD subphenotypes[63] and diagnosis[41,64,65], negative scores in social performance, perception and mentalizing tasks in schizophrenia patients[66], ADHD patients[67] and depressive temperament (as part of a haplotype block)[19]. Carriers of this allele also showed reduced mesolimbic reward system activation, a result that might point towards the neurobiological basis of the aforementioned phenotypic effects of this SNP[68].

Rs237889(T) has been associated with ASD, both as part of a deleterious haplotype[27] and independently[69], as well as with differences in moral judgment; carriers of the archaic C allele were more prone to give utilitarian answers in dilemmas[70]. Rs237897(A) is part of a haplotype related to ASD[27], altruism in males[30], lower self-reported betrayal levels[71], continuous social connectedness[72], and Theory of Mind[18]. Alleles of rs53576 have been reported in several studies: the G allele has been reported to be implicated in Bullimia Nervosa[73], but also in diminished stress after social support[74], adult separation anxiety[75], oxytocin sensitivity in social cooperation settings (increased in males, decreased in females)[76], overall weak social cognition skills in ADHD patients[25] and facial recognition deficits[53]. MHS rs53576(A) might be involved in ASD[27,45], higher empathic performance[77,78] and social connectedness in women[31], but also lower psychological resources such as self-esteem, optimism and emotional mastery[79]. Though the literature on rs53576 doesn't provide unequivocal results, there seems to be consensus on this SNP being dependent on environmental factors: the G allele appears to affect social sensitivity; adverse life conditions can lead to negative (non-prosocial) behavior in G carriers, but the opposite effect has also been reported[80]. Rs237917(T) is related to emotion recognition[81]. SNP rs2228485(A) is part of a haplotype related to loneliness[82] and overtransmitted in ASD[45]. Carriers of the G allele were more prone to give incorrect answers when required to identify negative emotions in male face

images[83].

Table 1. Allele distribution on the *OXTR*-SNPs in the species studied. Al: allele, Pop.: population, Ancestral: also found in Macaques, Bonobos, Chimpanzees. Ancestral: also found in bonobos. Homo: also found in Archaic (Neanderthals, Denisovans) and Modern Humans. Abbreviations: MH: Modern Humans, MHS: Modern Human-Specific, Neand: Neanderthals, Den: Denisovan, B: Bonobos, TFB: Transcription Factor Binding, LD: Linkage Disequilibrium.

SNP	Type	Al.	Pop.	Effect	Trial sample	Other remarks
rs2228485	Exonic	A	Ancestral	Loneliness[82]	285	Synonymous. A/G in Bonobos, A in Chimpanzees
				ASD[45]	195 (Chinese)	
		G	MHS (also present in B.)	Emotion recognition[83]		
rs237897	Intronic	G	Ancestral			G/A in Bonobos, G in Chimpanzees
		A	MHS (also present in B.)	ASD[27]	152	
				Altruism[30]	203	
				Lower self-reported betrayal levels[71]	165	
				Social connectedness[72]	11.000	
				Theory of Mind[18]	301	
rs11131149	Intronic	G	Ancestral	Theory of Mind, higher levels of social cognition[18]	350 children	
				Depressive mood[19]	493 (Japanese)	
		A	Homo	Lower levels of social cognition[18]	350 children	Present in macaque
rs59190448	Intronic	A	Ancestral			
		G	Homo	Anxiety, stress and depression risk[21]	653	Positive selection[20]
rs13316193	Intronic	T	Ancestral	ASD[27]	152	
				Depressive mood[19]	493 (Japanese)	Affects *OXTR* total expression in the brain[29]
				Poor empathic communication[28]	120	
		C	Homo	Empathy[22]	101(Chinese)	
				Poor social skills[25]	112	
				Greater cooperation and comforting[23]	422 (Chinese males)	
				ADHD[24]	276 ADHD patients	
				Face emotion recognition[26]	151 children with ADHD	
rs9872310	3' UTR	A	Ancestral			
		G	Homo	Altruism[30]	203	
				ASD[27]	152	
rs4686302	Exonic	C	Ancestral			Missense
		T	Homo	Better perspective taking skills[22]	101(Chinese)	
				Face emotion recognition[84]	151 children with ADHD	
				Social connectedness in men, opposite in women[31]	Over 11000 individuals	
rs237888	Intronic	C	Ancestral	IQ and VABS scores[27]	152	
				Altruism[30]	203	

		T	MH+Neand	Greater impairment of ASD[32]	1002 ASD patients	
				Methylation of CpG sites linked to abuse and psychiatric symptoms[33]	393 African American adults	
rs60902022	Intronic	T	Ancestral			May affect TFB through LD[34]
		C	MH+Neand			
rs6770632	3' UTR	A	Ancestral	Aggression[35]	160 children	
		G	MH+Altai	VABS scores[27]	152	
rs237885	Intronic	G	Ancestral	Altruism[30]	203	
		T	MH+Altai	ASD[36]	282 (Japanese)	
				Schizophrenia[37]	145	
				Callous/unemotional traits[35]	160 children	
				Higher risk of aggression[38]	488 cases, 488 control (Chinese)	
rs1042778	3' UTR	T	Ancestral	Lower levels of OXT in plasma, diminished parental care[39]	352	Affects *OXTR* transcription and translation processes, amygdalar expression[29,30]
				Panic and aggressive behaviors[40]		
				Recovery from low maternal emotional warmth[43]	2341	
		G	MH+Den	ASD[27,40,41]	152, 2333, 209	
				Aggression[35]	160 children	
				Prosocial fund allocations in the Dictator Game[30]	203	
				Might lower transcription levels of *OXTR*[40]		
				Altruism, comforting behavior[23]	422 Chinese males	
				Positive emotions after training[44]	122	
rs237911	5' UTR	A	Ancestral	ASD[36,45,46]	195 (Chinese), 282 (Japanese), 3941	A/C in macaque
		G	MH+Den			
rs2254298	Intronic	G	Ancestral	Lower communication[28]	120	
				Variation in empathy[22]	101 (Chinese)	
				Methylation at cg11589699 (increased depression and anxiety)[48]	393 (African American)	
				Less sensitive parenting and lower plasma OXT[39]	352	
				Higher positive affect[37]	352	
				Lower scores in depressive temperament[19]	493 (Japanese)	
				Higher levels of Retrospective Self-Report of Inhibition and Adult Separation Anxiety[56]	93 patients	
				Smaller left amygdala[61]	211 (men), 199 (women)	
		A	MH+Den	ASD[36,45,46]	195 (Chinese), 282 (Japanese), 3941	
				Lower levels of emotion recognition and resilience scores[55]	264 (Korean)	
				Increased amygdala volume[59]	55	

				Fewer social deficits in an ADHD sample more social deficits in an ASD sample[26]	341 (ASD patients), 276 (ADHD patients)	
				Lower serum OT in ASD patients[52]	55 (ASD patients), 110 (controls)	
				Positive parenting behavior, physically controlling behavior[50]	157 mothers	
				Reponsive to the impact of adversity[49]	302	
				High levels of physical aggresion[54]	197 (Chinese) adolescents	
				Vulnerability for antisocial behavior after maltreatment	1591	
rs53576	Intronic	G	Ancestral	Bullimia Nerviosa[73]	262 (Korean)	
				Diminished stress[74]	176 (77 Caucasian, 99 non-Caucasian)	
				Separation anxiety[75]	185	
				Oxytocin sensitivity in social cooperation settings (increased in males, decreased in females)[76]	204	
				Weak social cognition in ADHD[25]	112	
				Facial recognition deficits[53]	18 (Italian), 6 (German)	
		A	MHS	ASD[27,45]	195 (Chinese), 152	
				Empathy[77,78]	50, 192 (multiple ethnicities)	
				Lower psychological resources[79]	344	
				Social connectedness (women)[31]	Over 11000	
rs2268490	Intronic	C	Ancestral	Altruism[30]	203	
				Vocal alterations under stress[62]	657 (Finnish twins)	
		T	MHS	Stress-related vocal symptoms and higher cortisol levels[62]	657 (Finnish twins)	
rs2268493	Intronic	T	Ancestral	ASD[41,63–65]	417 (multiple ethnicities), 530 (Caucasian), 527, 2.333	Reduced mesolimbic reward system activation[68]
				Negative scores in social tasks in schizophrenia[66]	74	
				ADHD[67]	99	
				Depressive temperament[19]	493 (Japanese)	
		C	MHS			
rs237917	Intronic	C	Ancestral			
		T	MHS	Emotion recognition[81]	207 (Central European)	
rs237889	Intronic	C	Ancestral	Utilitarian answers in dilemmas[70]	228, 322	
		T	MHS			
				ASD[27]	152	

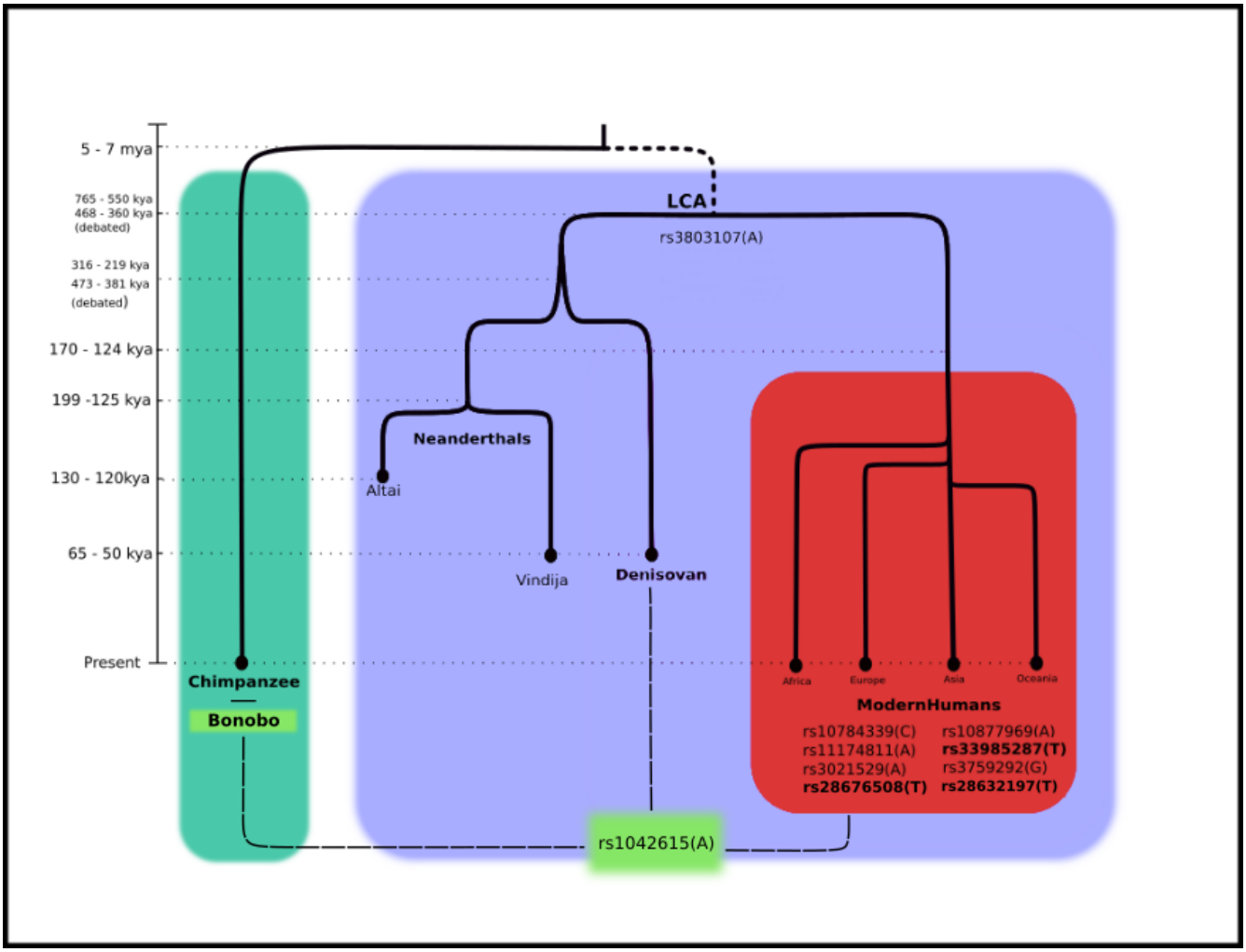

Figure 2. Evolutionary distribution of *AVPR1A* (regular) and *AVPR1B* (bold) alleles. The alleles displayed are the non-ancestral ones. LCA = Last Common Ancestor.

2.2 Vasopressin receptors

The distribution of vasopressin receptors is somewhat less complex than that of the oxytocin receptor. For example, we could not identify any sites that are both polymorphic in modern humans and different within the two neanderthals included in our study.

Only one modern human allele of *AVPR1A* was identified in both the Neanderthal and Denisovan genomes: rs3803107(A). Rs3803107(A) (3'-UTR) has been studied in relation to ASD in an Irish sample, but this correlation did not reach the level of significance[85]. Rs1042615(A), a synonymous variant of *AVPR1A*, also showed association with ASD in present-day humans[86] and often occurring vocal symptoms during stress[62], but in the ancient DNA sample it was only found in the Denisovan individual. Rs1042615(A) is the third site in this study that is also found in bonobos, constituting another potential convergent site.

The ancestral G allele of the 3'-UTR variant rs10784339 has been associated with stress reactivity and substance addiction risk[87,88], while the function of the MHS C allele is unknown. The ancestral C allele of rs11174811 (3'UTR) is related to substance addiction risk[87,88], but also to higher anxiety levels[89] and aggression[35]. The MHS variant disrupts a microRNA binding site, increasing the expression levels of *AVPR1A* and possibly affecting the anxiety relief consequences of vasopressin in anxious situations[88].

The ancestral G allele of rs3021529 may also be under balancing selection and affect the regulation of the gene[20], and has been linked to addiction[90]. The ancestral A allele of rs3759292 was found to be under directional selection[20], but without any reported functional implications. The MHS G allele has been linked to heroin addiction[91] and also to ASD[92]. Other alleles have been also studied in the context of social behavior and related disorders, especially ASD, such as the MHS rs10877969(A)

(intron variant)[92,93]. Concerning *AVPR1B*, rs28676508(T) has been claimed to be involved in child onset aggression[94]. The missense (arginine to histidine, position 364) variant rs28632197(T) has been associated with ASD diagnosis[63] and panic disorder[95]. Finally, the G allele of rs33985287 protects against depressive moods in female children[96].

Table 2. Allele distribution on the *AVPR1A*-SNPs in the species studied. Ancestral: Also found in Macaques, Bonobos, Chimpanzees. Ancestral: also found in bonobos. Homo: Found in Archaic (Neanderthals, Denisovans) and Modern Humans. Abbreviations: MH: Modern Humans, MHS: Modern Human- Specific, Neand: Neanderthals, Den: Denisovan. B: Bonobos.

SNP	Type	Alleles	Pop.	Effect	Trial sample	Other remarks
rs1042615	Exonic	G	Ancestral			Missense. G/A in Bonobos, G in Chimpanzees
		A	MHS+Den (also present in B.)	ASD[86]	205 (Finnish)	
rs3803107	3' UTR	G	Ancestral			
		A	Homo			
rs10784339	3' UTR	G	Ancestral	Stress reactivity and substance addiction risk[87,88]	852, 2231	
		C	MHS			
rs11174811	3' UTR	C	Ancestral	Substance addiction risk[87,88]	852, 2231	Possibly under balancing selection[20]
				Higher anxiety levels[89]	1090 (German)	Increases expression of *AVPR1A*
				Aggression[35]	160 children	
		A	MHS			
rs3021529	Intronic	G	Ancestral	Addiction[90]	1.050	Possibly under balancing selection[20]
		A	MHS			
rs10877969	Intronic	C	Ancestral			Except macaque (G)
		A	MHS	ASD[92,93]	151 Korean trios, 633	
rs3759292	Intronic	A	Ancestral			Positive selection[20]
		G	MHS			

3 Discussion

This study reports a total of 29 SNPs, 19 for *OXTR*, and 10 for *AVPR1A* and *AVPR1B*. Of these, 5 and 8 variants, respectively, are MHS, which means 80% of the total of mutations in the case of AVP receptor genes. In addition, 3 variants (2 for *OXTR*, 1 for *AVPR*) are putative convergent sites between modern humans and bonobos. Only some of these SNPs (rs59190448, rs3021529, rs11174811, and rs3759292) have been previously claimed to be under selection in modern humans. There is evidence linking some of the SNPs identified here with prosocial behaviors (rs237917, rs2268490, rs237885 [section 2.1]; rs11174811 and rs33985287 [section 2.2]). The rest of the SNPs are either neutral, give mixed results, or confer risk of some social behavior-disorder, mainly ASD. Some of the limitations of this study listed at the end of this article may contribute to these results.

The clearest pattern we detect concerns AVP receptors, specifically, *AVPR1A*. 3 of the 5 MHS alleles (on rs11174811, rs3021529, rs3759292, all of which have been associated with signals of selection) occur at very high frequencies in the global population (Table S2). Of these, the A allele of rs11174811 shows the clearest change towards prosocial effects (the archaic C allele is associated with negative phenotypes). Such a change from a more ancient allele linked to negative effects to a

Table 3. Allele distribution on the *AVPR1B*-SNPs in the species studied. Ancestral: Also found in Macaques, Bonobos, Chimpanzees. Ancestral: also found in bonobos. Ancestral(CB) also found in Chimpanzees and Bonobos. Homo: Found in Archaic (Neanderthals, Denisovans) and Modern Humans. Abbreviations: MH: Modern Humans, MHS: Modern Human- Specific, Neand: Neanderthals, Den: Denisovan.

SNP	Type	Alleles	Pop.	Effect	Trial sample	Other remarks
rs28676508	Exonic	C	Ancestral			Synonymous. C/G in Bonobo, Chimpanzee
		T	MHS	Child onset aggression[94]	177	
rs28632197	Exonic	C	Ancestral			Missense. C/G in Bonobo, Chimpanzee
		T	MHS	ASD[63] Panic disorder[95]	207 186 (German)	
rs33985287	3' UTR	C	Ancestral	Protects against depressive moods[96]	464 (children)	C/G in Bonobo, Chimpanzee[97]
		T	MHS			

MHS allele linked to positive effects occur five times in our data: three times for *AVPR1A* (rs10784339 G>C, rs11174811 C>A and rs3021529 G>A), and two for *OXTR* (rs2268493 T>C and rs237917 C>T). But of these changes, only the *AVPR1A* rs11174811(A) reaches near-fixation in modern human populations. Comparative work on chimpanzees and bonobos[98,99] has highlighted the relevance of OXT and AVP receptors, especially *AVPR1A*, to capture differences in social cognition. Our analysis points in the same direction for archaic vs. modern humans.

Our analysis of *OXTR* yields more mixed results. Only one MHS mutations (on rs237917) is associated with positive effects. As a matter of fact, some alleles associated with negative phenotypes (rs59190448, rs237911) occur at high frequences in several populations (Table S1). Other alleles that occur at high frequencies in most modern populations (rs9872310, rs4686302, rs2268493, rs33985287) lack clear phenotypical effects. While the change on rs4686302 could have boosted prosociality, our SNAP2 test showed that this site is most likely of no functional importance (82% accuracy).

Taken on its own, the evolutionary distribution of *OXTR* alleles could be taken to lend some support to hypotheses that argue for early changes in our lineage associated with prosocial behavior, unlike the changes on *AVPR1A* and *AVPR1B* that appear to be largely clustered in MHS. It is certainly compatible with hypotheses like the neurochemical hypothesis put forth in[10], or the series of pro-social steps defended in[6]. Although these accounts stress the role of other hormones in early changes in hominins (dopamine in the case of[10] and β-endorphines for[6]), all of these hormones (especially oxytocin and dopamine) are known to interact and reinforce each other's effects[16,100], so it could be that the early changes in *OXTR* identified here formed part of a broader set of changes, early in our clade, that set the stage for our prosocial profile.

Still, our results, especially those concerning the AVP receptors, also point to a distinct MHS social profile, which meshes well with the predictions of another working hypothesis that tries to account for modern humans' prosociality, the 'self-domestication hypothesis'. Advocates of this hypothesis[14,15,101], build their case on certain physiological and behavioral traits that modern humans share with domesticated animals to argue for a significant turning point exclusive of *Homo sapiens* on the prosocial continuum. Although he does not endorse the logic of self-domestication,[6] also recognizes a special transition corresponding to the emergence of our species. Among these traits, digit ratio—a measure of prenatal androgen exposure[102]—suggests that Neanderthals had higher prenatal androgen exposure than modern humans[103]. Interestingly, one study reports that the association between digit ratio and cognitive empathy is contingent on one of the *OXTR* SNPs (rs53576) we mentioned in the Results, showing a three-way association between testosterone, oxytocin and empathy[104]. In the context of the self-domestication hypothesis, it is worth pointing out that both oxytocin and vasopressin receptors have been found to be under relaxed selective constraint in domesticated species[105], and have been claimed to facilitate domestication[106].

Our results could be used as a springboard for other studies delving into the differences in prosociality between bonobos and chimpanzees, as well as for those studies looking into evidence for convergent evolution in bonobos and modern humans in an attempt to explain their similarities in terms of prosociality[107,108]. We found three alleles that bonobos and modern humans share (rs237897(A), rs2228485(G) and rs1042615(A)), while we did not find any for modern humans and chimpanzees. Of these only rs1042615(A) is a missense mutation, while rs2228485(G) is synonymous and rs237897(A) an intronic variant. Even though missense mutations tend to attract more scientific interest, there is accumulating evidence that synonymous SNPs can affect splicing or mRNA stability, thereby altering gene products[109]. The association studies on these sites give mixed

results, so it would be interesting to pursue these sites' functionality further in a larger bonobo sample.

Among the Neanderthals we found that only the Altai carried two present-day alleles which have been associated with antisocial behavior, such as ASD, schizophrenia, (female) aggression (section 2.1) and *OXTR* mRNA expression in the brain[25]. If it is the case that these SNPs were frequent and not a fabric of the small sample of ancient human DNA currently available, it could mean that within the general Neanderthal population, Altai Neanderthals might have been less social than their conspecifics of other populations. A less prosocial attitude would be consistent with the high inbreeding rates found in the genome of the Altai Neanderthal[11]. According to[110], Neanderthals were deeply subdivided into small population groups with scarce contact between them, which may have given them a social profile distinct from *Homo sapiens*.

SNPs present only in present-day humans and the Denisovan individual are of special interest considering the lack of archaeological information on Denisovans. According to paleogenomic studies, the rate of inbreeding of the sequenced individual is high, suggesting a very low population size alongside a two-fold increase of *H. Sapiens* competitor population size[13]. Some of these differences might be modulated by *OXTR* variation (rs1042778 and rs1042615 increase ASD-risk, while the first one also affects altruism positively (sections 2.1, 2.2)).

We acknowledge that there are limitations to this study. First, there are vastly more genomes currently available for the modern human population. While this may tip the balance towards modern human specificity in our study, the contrasting patterns obtained for oxytocin and vasopressin receptors suggest that our results cannot be fully reduced to the number of genomes available. Second, we have assumed that the SNPs studied would have the same (if any) effect on archaic humans or great apes, while their functionality has only been studied in modern humans. Since we are dealing with different genomic backgrounds, our interpretation remains tentative, although it is broadly compatible with information based on the fossil record and paleogenomic evidence (like inbreeding rates) or with behavioral differences between chimpanzees and bonobos. Also different plasticity windows have been hypothesized to play a role in susceptibility to both positive or negative influences[111]. Thus, it could be that the different ontogenetic trajectories that have been hypothesized for modern humans and Neanderthals[112] based on fossil evidence shaped a different susceptibility profile for them. Third, we have assumed that the ancient genomes that have been sequenced were representative of the general archaic population, something that might not be the case. Fourth, the allele-distribution data (Tables S1 and S2) we found in the literature for different modern human populations come from studies that have used different sample sizes, thus it might be that the high distribution of an allele is in reality a false positive. For this reason, we have limited our analysis of these tables to the Discussion. Fifth, all the sites that we considered here and labeled polymorphic in chimpanzees and bonobos (rs2228485, rs1042615, rs28676508, rs28632197, rs33985287) were in fact present with a 100% frequency in all the individuals of the SNV-data we used, but they differed from the allele present in the reference genomes. For this reason, in order to infer the ancestral state, we also made use of the gorilla and the orangutan genomes (apart from the macaque), which in all these sites showed the same variants as in the chimpanzee and bonobo reference genomes. Future research should use larger population samples to figure out the state of these sites. Sixth, our study may suffer from a publication bias where alleles with negative effects are overrepresented because of their clinical relevance. Finally, it could be said that our study favors oxytocin and vasopressin instead of other hormones, such as β-endorphines, cortisol, dopamine and testosterone, that have also been claimed to have been crucial in the evolution of our prosociality. While we have conveyed that there is enough theoretical ground to choose OXT and AVP for this study, we have also acknowledged that the role of oxytocin and vasopressin in prosociality depends on its interactions with other hormones that regulate social behavior.

4 Methods

We retrieved the *OXTR*, *AVPR1A* and *AVPR1B* DNA sequences from the following sources: the publicly available genomes of two Neanderthals and a Denisovan[11–13], seven high-coverage present-day human genomes (San(HGDP01036), Mbuti(HGDP00982), Karitiana(HGDP01015), Yoruba(HGDP00936), Dinka(DNK07), French(HGDP00533) and Han(HGDP00775) genomes, originally sequenced for[12]), 1000 Genomes project[113], manipulated through the Ensembl[114], the chimpanzee (*Pan Troglodytes*) genome (CHIMP2.1.4 version), the bonobo (*Pan Paniscus*) genome (PANPAN1.1, Max-Planck Institute for Evolutionary Anthropology version) and the rhesus macaque (*Macaca Mulatta*) genome publicly provided by Ensembl[114]. We also used Single Nucleotide Variant (SNV)-data found in[97] for 13 bonobos (Pan paniscus) and 25 chimpanzees covering from west to east Africa (10 *Pan troglodytes ellioti*, 6 *Pan troglodytes schweinfurthii*, 4 *Pan troglodytes troglodytes*, 4 *Pan troglodytes verus*, and 1 chimpanzee hybrid).

Alignments were performed with the following tools: the built-in Ensembl tool[114], the Max Planck for Evolutionary Anthropology Ancient Genome Browser (https://bioinf.eva.mpg.de/jbrowse/), Aliview[115], Decipher for R[116], Bedtools, MUSCLE[117] and MView[118]. We used all the genomic sequence of the genes we aligned, as provided in the standard layout of the files of the genomic sequences in the Ensemble database, namely with 600 bp upstream and downstream. We defined the genomic sequences in the same way when we extracted the gene sequences from the archaic genomes. We found no gaps in the gene sequences we studied in archaic humans (Altai and Vindija Neanderthals and Denisovans). We used the Integrative Genomics Viewer (IGV)[119] to search for the relevant SNP-positions in the bonobo and chimpanzee SNV-data.

We first aligned the modern human gene sequences of *OXTR*, *AVPR1A* and *AVPR1B* against each archaic human gene sequence and of the differences we found, we focused on those which are polymorphic in modern humans. We then aligned the modern human sequences *OXTR*, *AVPR1A* and *AVPR1B* against the chimpanzee, bonobo and macaque sequences in order to infer the ancestral state of previously identified sites (Table S5). The SNV-data from bonobos and chimpanzees were aligned to the *hg38*; we searched ad hoc for the locations of the SNPs of interest to account for variation in these sites. All alleles we studied were present with a 100% frequency in the SNV-data. When the allele found in the SNV-data was different from the allele present in the reference genomes (as in rs2228485, rs1042615, rs28676508, rs28632197, rs33985287), we reported both alleles and considered this site polymorphic. In order to infer the ancestral allele for these specific sites, we aligned the aforementioned SNPs with the orangutan (*Pongo abelii*) genome (PPYG2version) and the gorilla (*Gorilla gorilla gorilla*) genome (gorGor4 version) through Ensembl[114]. We used the same database when we wanted to assess the state of a specific variant in the rest of primates in the cases of convergence between modern humans and bonobo.

We then classified the alleles in evolutionary stages based on their distribution (presence or absence) in the different species/populations studied (e.g. Homo-specific, modern human-specific, Altai Neanderthal-specific). We then reviewed exhaustively the clinical significance of each one of these SNPs in present-day human populations. The literature filtering was performed through the Viewer tool of the National Center for Biotechnology Information[120]. SNPs not known to be related to social cognition, social disorders or any other relevant information were discarded. Specifically, of the 3160 single nucleotide variants identified on the *OXTR*, only 55 are mentioned in the literature. Of those, we included 19 in our study (34,54%). Of the 1375 single nucleotide variants identified on *AVPR1A*, 10 are mentioned in the literature. Of those, we included 7 (70%). And of the 988 single nucleotide variants identified on *AVPR1B*, 14 are mentioned in the literature. Of those, we included 3 (21,42%). The reader can find a full list of the SNPs that have been identified in modern humans on the genes studied, as well as a list of the archaic-specific polymorphisms known to date in the Supplementary Material (Tables S3-4).

In addition, we performed a transcription factor binding site prediction test using Lasagna2.0[121], and functional effects tests of exon variants with SNAP2[122] to all the variant-changes we had identified between modern and archaic human sequences. The Lasagna2.0 test did not yield any results.

We also multialigned all the gene sequences (*OXTR*, *AVPR1A* and *AVPR1B*) using only the reference genome sequences of the species included in the study: Human (GRCh38.p12), Neanderthal and Denisovan[11–13], the chimpanzee genome (Pan_tro_3.0), the bonobo genome (PANPAN1.1, Max-Planck Institute for Evolutionary Anthropology version) and the rhesus macaque genome (Mmul_8.0.1) publicly provided by Ensembl[114] (Suppl. Material).

We also included in our analysis several *AVPR1A*-microsatellites that have been associated with social-related phenotypes in the literature. More specifically we added as a sequence-search track the modern human RS3-$(CT)_4TT(CT)_8(GT)_{24}$, RS1-$(GATA)_{14}$, GT_{25} and the intronic AVR-$(GT)_{14}(GA)_{13}(A)_8$ microsatellite-sequences on the jbrowser (https://bioinf.eva.mpg.de/jbrowse/) and on the Integrative Genomics Viewer and looked for any possible differences in the Neanderthal (Altai and Vindija) and the Denisovan sequences. We did not find any changes in these regions, hence we did not make any further mention to this in the Results.

Acknowledgements

We thank Thomas O'Rourke for comments on the manuscript. We also thank Erich D. Jarvis and Evan E. Eichler for guidance on primate variation data.

Funding statement

CB acknowledges the financial support from the Spanish Ministry of Economy and Competitiveness/FEDER funds (grant FFI2016-78034-C2-1-P), a Marie Curie International Reintegration Grant from the European Union (PIRG-GA-2009-256413), research funds from the Fundació Bosch i Gimpera, from the Generalitat de Catalunya (2017-SGR-341), and the MEXT/JSPS Grant-in-Aid for Scientific Research on Innovative Areas 4903 (Evolinguistics: JP17H06379). CTh acknowledges support from the Generalitat de Catalunya in the form of a doctoral (FI) fellowship. AA acknowledges financial support from the Spanish Ministry of Economy and Competitiveness and the European Social Fund (BES-2017-080366).

Author Contributions Statement

CTh conceptualized and designed the study. AA ran all the tests, did the literature mining, generated the figures, and tables; CTh and AA ran the multialignment and handled the primate SNV-data; CB coordinated the study; CTh, AA and CB wrote the paper.

Data availability statement

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Additional Information

Competing interests

There is NO Competing financial or non-financial interest.

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