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A polymorphic indel containing the RS3 microsatellite in the 5′ flanking region of the vasopressin V1a receptor gene is associated with chimpanzee (*Pan troglodytes*) personality

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Vasopressin is a neuropeptide that has been strongly implicated in the development and evolution of complex social relations and cognition in mammals. Recent studies in voles have shown that polymorphic variation in the promoter region of the arginine vasopressin V1a receptor gene (*avpr1a*) is associated with different dimensions of sociality. In humans, variation in a repetitive sequence element in the 5′ flanking region of the *AVPR1A*, known as RS3, have also been associated with variation in *AVPR1a* gene expression, brain activity and social behavior. Here, we examined the association of polymorphic variation in this same 5′ flanking region of the *AVPR1A* on subjective ratings of personality in a sample of 83 chimpanzees (*Pan troglodytes*). Initial analyses indicated that 34 females and 19 males were homozygous for the short allele, which lacks RS3 (DupB$^{-/-}$), while 18 females and 12 males were heterozygous and thus had one copy of the long allele containing RS3 (DupB$^{+/-}$), yielding overall allelic frequencies of 0.82 for the DupB^{-} allele and 0.18 for the DupB^{+} allele. DupB$^{+/+}$ chimpanzees were excluded from the analysis because of the limited number of individuals. Results indicated no significant sex difference in personality between chimpanzees homozygous for the deletion of the RS3-containing DupB region (DupB$^{-/-}$); however, among chimpanzees carrying one allele with the DupB present (DupB$^{+/-}$), males had significantly higher dominance and lower conscientiousness scores than females. These findings are the first evidence showing that the *AVPR1A* gene plays a role in different aspects of personality in male and female chimpanzees.

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Vasopressin is a neuropeptide with multiple physiological functions that has been strongly implicated in the development and evolution of complex social relations and cognition in mammals (Donaldson & Young 2008; Goodson & Bass 2001). Studies in several species have shown that one of three known AVP receptors, arginine vasopressin V1a receptor (AVPR1A), is expressed in the brain and plays a prominent role in producing diversity in social behavior, in addition to its role in regulation of vasoconstriction. For example, meadow and prairie voles, which differ dramatically in their pair-bonding behavior, show pronounced differences in AVPR1A expression patterns in the brain (Lim *et al*. 2004, 2005). More recently, several studies in voles have examined variation in behavior and AVPR1A expression in relation to microsatellite length in the promoter region of the V1a receptor gene (*avpr1a*). There are both individual and species differences in *avpr1a* expression and these have been associated with variation in pair bonding and other dimensions of social behavior in voles (Hammock & Young 2005, 2006; Hammock *et al*. 2005; Young & Wang 2004). Variation in this polymorphic microsatellite has also been shown to affect *avpr1a* gene transcription in cell transcription from *in vitro* reporter assays (Hammock & Young 2004).

In primates, less is known about the functional role of *AVPR1A* in social behavior but recent studies have shown considerable polymorphic variation in the *AVPR1A* gene analogous to that seen in voles, suggesting that individual and species differences in sociality may be associated with this gene (Babb *et al*. 2010; Donaldson *et al*. 2008; Rosso *et al*. 2008). In human *AVPR1A,* variation in repetitive microsatellite element RS3 (see Fig. 1) located in the 5′ flanking region of the gene has been linked to variation in social behavior, including altruistic behavior, and pair-bonding-related behavior in males (Donaldson *et al*. 2008; Meyer-Lindenberg *et al*. 2011; Walum *et al*. 2008). It has also been suggested that *AVPR1A* may be a candidate susceptibility gene for autism,

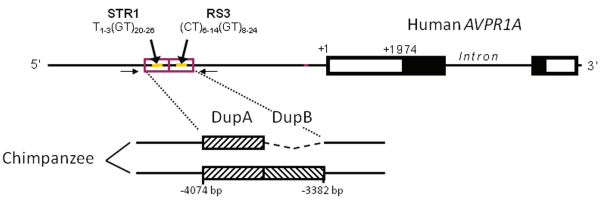

Figure 1: Schematic of the polymorphic microsatellite elements in the primate *AVPR1A* locus. Two repeat motifs (DupA and DupB) in tandem containing repetitive microsatellite elements (STR1 and RS3) are found in the 5′ flanking region of the human *AVPR1A*. Variation in the length of RS3 is associated with social behavior in humans, including social cognition in autism spectrum disorder (ASD). Chimpanzees are polymorphic at this site, with a significant proportion having the entire DupB, including RS3 deleted (short). Adapted from Donaldson *et al*. 2008.

a spectrum of neurodevelopmental disorders marked by problems in the development of normal social relationships and socio-cognitive abilities (Melke 2008). Likewise, *AVPR1A* variation in RS3 is related to activation of the amygdala during a face recognition task (Meyer-Lindenberg *et al*. 2008). Finally, variation in the length of RS3 has been associated with variation in *AVPR1A* gene expression in the human brain (Knafo *et al*. 2008) and in transcription reporter assays in cell culture (Tansey *et al*. 2011). Thus, our understanding of variation in sociality and cognitive processes as they relate to social cues and processes might benefit from further studies on the *AVPR1A* gene.

In this study, we examined the association of an indel containing RS3 upstream of the *AVPR1A* gene with individual differences in personality in captive chimpanzees (*Pan troglodytes*). Chimpanzees are an excellent model to explore the functional role of the RS3 polymorphism in the *AVPR1A* gene because there is a common indel resulting in a complete deletion of the RS3 sequence in 80% of the chimpanzee alleles (Donaldson *et al*. 2008). Within humans, the RS3 repeat region is housed within a larger, ∼350 bp tandem duplicated region. The first of these duplicated regions, DupA, spans −3730 to −4074 bp relative to the transcription start site and contains a GT_{20-26} microsatellite, known as STR1. The second block, DupB, spans −3382 to −3729 bp and contains the complex microsatellite, RS3 $[(CT)_{6-14}(GT)_{8-24}]$ (Fig. 1). Chimpanzees are polymorphic for the presence of the RS3-containing DupB region, leading to a 357-bp difference between the $DupB^{+}$ and Dup^{-} alleles (Donaldson *et al*. 2008). The deletion of RS3 in some individuals makes this species ideal for assessing the potential role of the *AVPR1a* gene, and more specifically RS3, on sociality and related processes (i.e. social cognition).

To assess the association between *the RS3 DupB indel* and personality in the chimpanzees, we compared a sample of individuals who were either homozygous for the deletion ($DupB^{-/-}$) or were heterozygous and had one DupB-containing allele ($DupB^{+/-}$) on subjective personality ratings. Previous studies have shown that chimpanzees, like humans, have different personalities, which include what has been described as the five-factor model (Digman 1990) or 'Big 5' personality dimensions in humans (extraversion, agreeableness, conscientiousness, neuroticism and openness). In addition, chimpanzees have a sixth personality dimension, dominance, which is seemingly related to competitive prowess (King & Figueredo 1997). Despite the recent comparative interest in personality among nonhuman animals (Freeman & Gosling 2010; Gosling 2001), to date the majority of studies have focused on the description and construction of personality factors in nonhuman animals (Gosling 2001), whereas very few studies have examined the potential role of genetic factors on individual differences in personality. In the only study in chimpanzees, Hong *et al*. (2011) found that polymorphic variation in a gene that encodes tryptophan hydroxylase 2 (*TPH2*), an enzyme involved in the production of serotonin, was linked to variation in neuroticism.

In the current study, we sought to examine whether variation in personality was associated with the *AVPR1A* 5′ flanking region polymorphism, given its reported important role in sociality. This was accomplished by combining recently published data on personality in a sample of chimpanzees housed at the Yerkes National Primate Center (Weiss *et al*. 2007) with the vasopressin genotype data that were reported in a subsample of these same individuals (Donaldson *et al*. 2008). Thus, we combined the genetic data with the extant personality ratings to assess whether differences in personality were related to the presence or absence of the RS3-containing DupB element in the *AVPR1A* 5′ flanking region. If the *AVPR1A* 5′ flanking region plays a role in personality in chimpanzees, then significant differences should be evident in one or more of the traits in chimpanzees with different genotypes.

Methods

Subjects

All chimpanzees were members of the colony of apes housed at the Yerkes National Primate Research Center (YNPRC). DNA samples and associated personality rating scores were available in 83 adult and sub-adult chimpanzees including 52 females and 31 males. All aspects of this research adhered to the American Psychological Associations guidelines for the ethical treatment of animals in research.

Personality assessment

We used the personality measures reported by Weiss *et al*. (2007), which included chimpanzees housed at the YNPRC. Briefly, in the Weiss *et al*. (2007) paper, personality was assessed using the chimpanzee personality questionnaire (CPQ) which consists of a 43 adjective questionnaire items used by observers to rate their overall impressions of the chimpanzee's behaviors (a freely available copy can be found at http://extras.springer.com/2011/978-1-4614-0175-9). For example, the adjective 'cautious' is defined as subject that often seems attentive to harm or danger from its actions and avoids risky behaviors. Individual adjectives, reflecting traits in the behavior of the animals, were rated on a scale from 1 to 7, where 1 indicated the absence of that trait and 7 indicated high frequency in the expression of that trait. The CPQ has been shown to be both reliable and valid with interrater reliabilities ranging from 0.71 to 0.88 (King & Figueredo 1997; King *et al*. 2005). Weiss *et al*. (2007) described four personality factors in chimpanzees: dominance (D_{CH}), extraversion (E_{CH}), conscientiousness (C_{CH}) and agreeableness (A_{CH}) that were stable and replicable across different samples of chimpanzees including individuals living in zoos in comparison to those housed at the YNPRC.

Table 1: Item traits loading on each personality factor

Trait	Dominance	Extraversion	Conscientiousness	Agreeableness
Positive items				
	Dominant	Active	Stable	Gentle
	Persistent	Playful	Predictable	Sociable
	Bullying	Sociable		Friendly
	Independent	Inquisitive		Affectionate
	Decisive	Friendly		Stable
	Aggressive	Inventive		Predictable
	Defiant	Affectionate		Sensitive
	Stingy			Helpful
	Manipulative			Protective
				Intelligent
				Sympathetic
Negative items				
	Submissive	Lazy	Aggressive	
	Dependent	Solitary	Defiant	
	Timid	Depressed	Depressed	
	Fearful	Unemotional	Erratic	
	Cautious		Impulsive	
			Excitable	
			Jealous	
			Disorganized	
			Autistic	
			Irritable	
			Reckless	
			Clumsy	

The data are taken from Weiss *et al*. (2007).

The item loadings for each trait reported by Weiss *et al*. (2007) are shown in Table 1. The factor scores were unit weighted and converted into *T*-scores with a mean of 50 and a standard deviation of 10. Thus, *T*-scores over 50 indicate that a subject has more than the average dimension of that trait, whereas values lower than 50 indicated that subjects had lower-than-average characteristics of that trait. The individual *T*-scores as well as the 43 item-specific ratings collected in the Weiss *et al*. study were used in the analyses in this study.

DNA extraction, genotyping and analysis

DNA samples were isolated from buccal swabs or blood samples using Puregene DNA purification system (Gentra, Minneapolis, MN, USA) as described by Donaldson *et al*. (2008). Following extraction, stock DNA was separated into three aliquots: one for onsite storage at −80°C, one for offsite storage, and a working stock for genotyping. Samples were tracked via a secure Filemaker Pro 8 database that linked sample codes for each aliquot, demographics for each subject (e.g. subject number, birth date, sire, dam, etc.), DNA quantification and purity analysis results, and genotype data.

Each individual was genotyped for the *AVPR1A* DupA/B region using the primers and conditions reported in previous studies with slight modifications (Donaldson *et al*. 2008). Briefly, we used forward primer 5′-GCATGGTAGCCTCTCTTTAAT and a reverse primer of 5′-CATACACATGGAAAGCACCTAA with an annealing temperature of 57°C for 30 cycles: 95°C, 5 min; 30×(95°C, 30 seconds; 57°C, 30 seconds; 72°C, 3 min; 72°C, 10 min; 4°C, hold). Polymerase chain reaction (PCR) amplification was undertaken using the Epicentre Failsafe kit using premix H (Illumina Inc., Madison, WI, USA) according to the manufacturer's directions. Genotyping was performed in a volume of 20 μl containing 20 ng target genomic DNA. PCR products were resolved on a 2% agarose gel (SeaKem Agarose LE, Lonza, Basel, Switzerland) at 100 V for 45 min with a 100-bp DNA ladder (New England Biolabs, Ipswich, MA, USA) in tris-borate-EDTA (TBE). The DupB-containing allele resulted in a band of ∼900 bp, while the DupB minus allele was ∼570 bp long, and genotypes were visually assigned (Donaldson *et al*. 2008). All genotypes were run in duplicate with gel analysis and were checked by the authors before the data set was finalized ($N = 130$).

Results

Allelic frequencies

Thirty-four females and 19 males were homozygous for the short allele ($DupB^{-/-}$), while 18 females and 12 males were heterozygous and thus had the long allele ($DupB^{+/-}$), yielding overall allelic frequencies of 0.64 for the $DupB^{-}$ allele and 0.36 for the $DupB^{+}$ allele. These frequencies are consistent with those previously identified in wild-caught chimpanzees (Donaldson *et al*. 2008). On the basis of these allelic frequencies, only 3.24% of the population is expected to be homozygous for $DupB^{+}$ allele. While we did not identify any homozygous $DupB^{+/+}$ individuals in this particular population, our distribution of genotypes is not significantly different from the number of individuals expected to carry these genotypes according to the Hardy Weinberg equation X^2 (2, $N = 130$) = 0.03, n.s.

AVPR1A variation and personality

We compared the factor scores using analysis of covariance (ANCOVA) with sex (male, female) and DupB genotype ($DupB^{+/-}$, $DupB^{-/-}$) as between-group factors while the relatedness coefficients served as a covariate. Relatedness

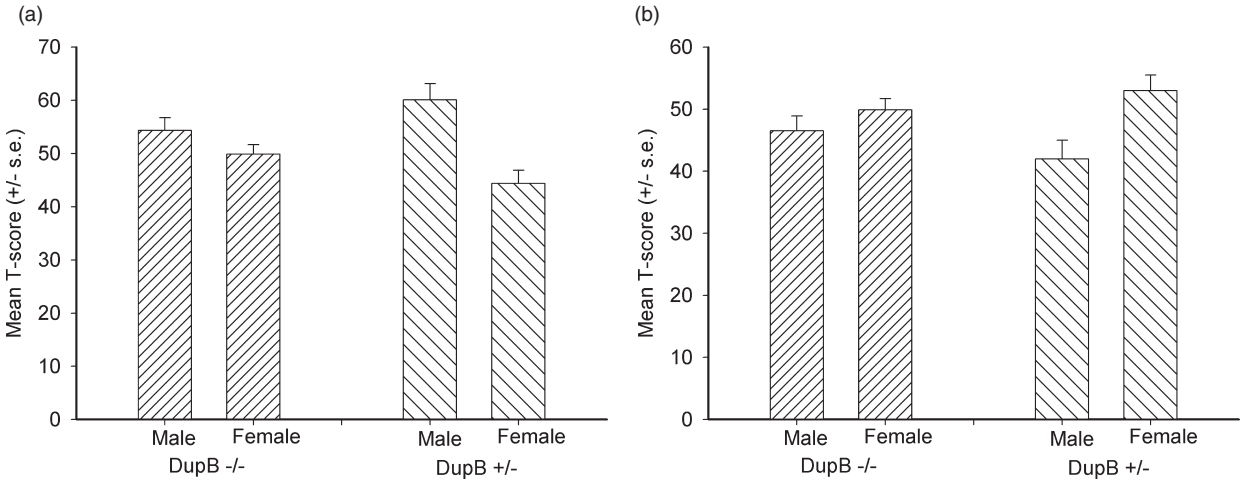

Figure 2: Sex by *AVPR1A* interactions on personality. Mean *T*-scores (±SE) for the (a) dominance and (b) conscientiousness traits for male and female DupB$^{+/-}$ and DupB$^{-/-}$ chimpanzees.

coefficients were used to determine the degree of relatedness of each individual to all other individuals in the YNPRC chimpanzee pedigree analysis. A significant three-way interaction was found between DupB genotype, sex and personality factor $F_{3,216} = 4.43$, $P < 0.005$. To further breakdown this interaction, we performed univariate *F*-tests with each personality factor serving as a dependent measure while sex and genotype served as between-group factors.

Significant two-way interactions between sex and DupB genotype were found for dominance $F_{1,79} = 5.133$, $P < 0.03$ and conscientiousness $F_{1,79} = 4.33$, $P < 0.05$. The mean *T*-score for dominance and conscientiousness for male and female DupB$^{+/-}$ and DupB$^{-/-}$chimpanzees are shown in Fig. 2. Post hoc analysis using Tukey's honestly significant difference (HSD) indicated that for dominance, no significant difference was found between DupB$^{-/-}$ males and females. However, DupB$^{+/-}$males had significantly higher dominance *T*-scores than DupB$^{+/-}$ females. In contrast, for conscientiousness, post hoc analysis showed no significant difference between DupB$^{-/-}$ males and females. However, DupB$^{+/-}$ males showed significantly less conscientiousness than DupB$^{+/-}$ females. Thus, sex differences in these personality dimensions only emerged in chimpanzees carrying the RS3 allele. No significant main effects or interactions were found for extraversion or agreeableness.

Item rankings and AVPR1A

We next considered whether sex and genotype differences were evident for each item on the CPQ. When considering the individual personality item rankings, we compared males and females within each genotype using a Mann–Whitney *U*-test because the data were on a ranked scale of measurement (see Table 2). For the DupB$^{-/-}$ chimpanzees, significant sex differences were found for only three items including fearful, active and aggressive. Females were ranked as more fearful while males were ranked as more active and aggressive. For the DupB$^{+/-}$ chimpanzees, significant sex differences were found for 18 items. Females were found to be more fearful, cautious, timid, sympathetic, submissive and dependent than males. In contrast, males were found to be more dominant, persistent, reckless, playful, active, bullying, aggressive, manipulative, excitable, impulsive, defiant and erratic than females.

Discussion

Chimpanzees with different polymorphisms in the 5′ flanking region of the *AVPR1A* promoter region show significant differences in the personality traits of dominance and conscientiousness. Moreover, the influence of this polymorphism on personality differs in males and females. DupB$^{+/-}$ males had higher dominance and lower conscientiousness scores than DupB$^{+/-}$ females. No significant differences in dominance or conscientiousness were found between DupB$^{-/-}$ females and males. Thus, the sex differences in these traits depend on the presence of the RS3-containing DupB element. Not surprisingly, the DupB genotype by sex interaction on personality generalized to several items that loaded on the dominance and conscientiousness factors (see Table 2). In short, significant sex differences were found in 18 traits within the Dup$^{+/-}$ chimpanzees, whereas only 3 items differed significantly between males and females within the Dup$^{-/-}$ subjects. Moreover, the sex differences found within the Dup$^{-/-}$ cohort were similarly found in the Dup$^{+/-}$ chimpanzees. Thus, the sex differences in personality found for the remaining 15 items were evident only in the Dup$^{+/-}$ cohort of chimpanzees.

Dominance in chimpanzees is complicated, and a number of factors or 'styles' of behavioral interactions can influence the development and maintenance of rank (Foster *et al*. 2009). Dominant males are typically more aggressive and show higher levels of testosterone than lower-ranking males,

Table 2: Mean rank score on each of the 43 personality items in male and female chimpanzees with the $Dup^{-/-}$ and $Dup^{+/-}$ genotype

	$Dup^{-/-}$		$Dup^{+/-}$	
Item	Female	Male	Female	Male
Fearful	**3.78**	**2.89**	**3.78**	**2.42**
Dominant	3.67	4.18	**2.94**	**5.13**
Personable	4.51	4.55	**3.86**	**4.92**
Cautious	4.10	3.55	**4.97**	**2.54**
Stable	3.99	3.74	4.11	3.63
Autistic	2.03	2.24	2.50	3.67
Stingy	4.07	3.58	3.22	4.08
Jealous	3.74	4.42	3.58	4.38
Reckless	3.29	3.68	**2.14**	**4.38**
Sociable	3.93	4.11	4.31	4.00
Timid	3.54	2.79	**3.94**	**2.54**
Sympathetic	3.24	3.16	**4.19**	**3.13**
Playful	3.19	4.03	**3.06**	**4.17**
Solitary	3.90	3.13	3.53	3.58
Active	**3.63**	**4.68**	**3.28**	**4.58**
Helpful	3.25	3.74	3.94	3.50
Bullying	3.49	4.08	**2.61**	**4.54**
Aggressive	**2.94**	**3.76**	**2.11**	**4.58**
Manipulative	4.01	3.74	**3.17**	**4.42**
Gentle	3.93	3.66	4.69	3.96
Affectionate	3.81	3.84	4.14	3.92
Excitable	3.75	4.05	**3.47**	**4.83**
Impulsive	3.34	3.26	**2.83**	**4.50**
Inquisitive	3.84	4.11	3.78	4.46
Submissive	3.72	3.11	**4.36**	**2.29**
Dependent	3.84	3.16	**4.06**	**2.25**
Irritable	3.59	3.34	2.86	3.79
Predictable	4.65	4.32	5.22	4.58
Decisive	4.63	4.42	4.00	4.42
Depressed	3.10	2.66	3.33	3.08
Sensitive	4.15	4.05	4.39	3.79
Defiant	3.50	3.55	**2.64**	**4.46**
Intelligent	4.34	4.03	4.39	4.29
Protective	3.44	3.39	3.83	3.62
Inventive	3.22	3.71	3.08	4.40
Clumsy	2.69	2.62	2.86	2.83
Erratic	2.88	3.45	**2.58**	**3.73**
Friendly	3.88	4.18	4.53	3.88
Lazy	3.41	2.97	4.00	3.13
Disorganized	2.79	3.34	3.06	3.25
Unemotional	3.50	2.82	3.14	2.67
Imitative	3.21	3.13	3.58	2.29
Independent	4.32	4.82	4.19	5.13

Bold values indicate a significant sex difference as showed by a Mann–Whitney *U*-test at $P < 0.05$.

particularly in the presence of estrous females (Pusey *et al*. 1997). Notwithstanding, smaller males can achieve high ranking status by engaging in a significant amount of socially affiliative behaviors, notably grooming with many members of the group (Foster *et al*. 2009). Thus, at least in males, no single behavioral trait or style necessarily predicts whether an individual will eventually achieve a high or low dominance rank. In female chimpanzees, no obvious linear dominance hierarchies are always found, which is in contrast to other group-living primates (Pusey *et al*. 1997; Wittig & Boesch 2003). Thus, in chimpanzees, it is likely that the mechanisms that underlie dominance differ between males and females. Our results suggest that polymorphic variation in the *AVPR1A* promoter regions may be an important variable in the mediation of dominance behavior chimpanzees, particularly among males.

Direct studies examining the role of *AVPR1A* variation and personality in humans, at least as measured by comparable tests to those used in this study with the chimpanzees, are lacking and therefore direct comparisons between species cannot be performed. However, several studies in humans have shown that polymorphisms in the RS3 region of *AVPR1A* are linked to some dimensions of social behavior such as novelty seeking and harm avoidance (Ebstein 2006), male pair bonding and relationship quality (Meyer-Lindenberg *et al*. 2008; Prichard *et al*. 2007; Walum *et al*. 2008), altruism (Avinun *et al*. 2011), expressive dance and communication, as well as interests in music (Bachner-Melman *et al*. 2005; Ukkola-Vuoti *et al*. 2011).

Vasopressin systems within the brain are sexually dimorphic, and vasopressin is expressed at higher levels in males than in females (De Vries *et al*. 1992). Vasopressin is thought to regulate behaviors in sex-specific manner, typically regulating male typical social behaviors. Thus, one would predict that genetic variation in AVPR1 would result in sex-specific effects on social behaviors. In at least one study, the effect of RS3 polymorphisms on human relationship quality was sex-specific, with the association being present in males but not females (Walum *et al*. 2008). It has also been shown that intranasal administration of vasopressin increases agonistic facial expressions in response to unfamiliar faces and decreases perceptions of friendliness in men, whereas in women, vasopressin administration elicits the opposite pattern of response (Thompson *et al*. 2006). Furthermore, intranasal vasopressin selectively impairs emotion recognition in men (Uzefovsky *et al*. 2012). This result is particularly intriguing in light of our finding of sexually dimorphic effects of DupB on several traits in apes.

Studies in voles have shown that individual differences in the *avpr1a* 5′ flanking region are associated with approach to novel odors and the formation of pair bonds and partner preferences (Hammock & Young 2005). Furthermore, central administration of vasopressin in male prairie voles selectively increases aggression and territoriality (Winslow *et al*. 1993), traits that seem to overlap with the items loading on the dominance factor in chimpanzees (see Tables 1 and 2). Vasopressin appears to have a conserved role in modulating the response to social cues in a sex-specific manner in a variety of species, regardless of the modality of those cues (Donaldson & Young 2008; Goodson and Bass 2001).

The extent to which traits, such as dominance and conscientiousness, are manifest in these types of social behaviors is unclear but this should be the focus of additional studies. Certainly one could argue that lower scores on certain adjectives such as 'fearful' or 'cautious' in the $DupB^{-/-}$ chimpanzees would suggest that $DupB^{+/-}$ individuals exhibit more of these traits which would manifest

itself as more exploratory to novelty but, as previously stated, this awaits future testing using behavioral paradigms.

In summary, as far as we know, these are the first evidence of the influence of polymorphisms in the *AVPR1A* gene on behavioral profiles of chimpanzees and, in fact, nonhuman primates. The findings reported here should be viewed as an initial report that warrants further study, with a specific emphasis on overt behavioral responses and profiles of individual chimpanzees with different *AVPR1A* polymorphisms. It would be particularly interesting to determine whether DupB$^{+/-}$and DupB$^{-/-}$ chimpanzees differ in the expression of the *AVPR1a* gene in the brain, because polymorphisms in the RS3 have been associated with variation in gene expression in the human brain as well as in *in vitro* transcription reporter assays (Knafo *et al*. 2008; Tansey *et al*. 2011). At this point we cannot conclude that the differences that we see in behaviors in our study are due directly to differences in gene expression caused by the presence or absence of the DupB region. It is possible that these polymorphisms are linked to other polymorphisms in the *AVPR1A* that are directly affecting AVPR1A expression or functionality. Regardless, our data does support the hypothesis that genetic variation at this locus is associated with variation in social behaviors. Moreover, as the chimpanzee genome has been mapped and publicly available for 6 years (Consortium 2005) and recently updated (CGSC 2.1.3 panTro3), the potential for evaluating the influence of additional genes on social behavior of chimpanzees as they relate to human typical and atypical behavior should be a focus of continuing research efforts.

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