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Rapid Communication

Genetic Diversity of Microsatellite RS3 in *AVPR1a* Promoter Region in Primates

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Abstract

The neurohypophyseal hormone Arginine Vasopressin (AVP) and its receptor type 1a (*AVPR1a*) play important roles in the modulation of social behaviors in mammals. RS3 microsatellites in the *AVPR1a* promoter region have been implicated in influencing social behavior. However, the relationship between RS3 diversity and social monogamy in primates is not clear. In this study, RS3 sequences from 18 primate species and 24 individuals were collected and aligned, and association between RS3 and social monogamy were analyzed. Though genetic diversity of RS3 was found in these animals, no significant association was observed here ($P > 0.05$). Results in this study enhance the appreciation of genetic diversity in the mammalian *AVPR1a* system, and set the stage for studies in the molecular diversity of the neurohypophysial hormones and social behavior in primates.

Keywords: Neuropeptide; RS3; Monogamy; Primate

Abbreviations

AVP: Arginine Vasopressin; *AVPR1a*: Arginine Vasopressin Receptor Type 1a; NWM: New World Monkeys; RS3: Microsatellites in *AVPR1a* promoter

Introduction

The neurohypophysial hormone Arginine Vasopressin (AVP) is synthesizedprimarily in the Paraventricular Nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. Through its two centrally expressed receptor subtypes (*AVPR1a* and *AVPR1b*), AVP has a variety of neurological effects on the social behaviors [1-4]. In primates, male titi monkeys receiving intranasal AVP treatments contacted their partner more frequently than the stranger [5]. Intranasal delivery of AVP has also been reported to affect social communication processes in men and women [6].

Of these two centrally expressed receptors, *AVPR1a* plays a more prominent role in vasopressinergic modulation of social behavior. Brain *AVPR1a* distribution differs considerably between monogamous voles (prairie voles) and non-monogamous voles (montane and meadow voles) [7] and forebrain *AVPR1a* expression is associated with sexual and social fidelity in male prairie voles [8]. For brain *AVPR1a* density, down-regulation of *AVPR1a* density resulted in a clear impairment in the preference for a mated female partner and a reduction in anxiety-like behavior in adulthood [9]. Central *AVPR1a* activation is necessary for both partner preference formation and expression in male prairie voles [10]. Increased brain *AVPR1a* density enhanced the partner preference of meadow voles [11]. Male marmosets show paternal behavior, and the prefrontal cortex of marmoset fathers display increased density of dendritic spines and enhanced expression of *AVPR1a* in these spines [12], suggesting that *AVPR1a* plays a role in paternal care. Note that genetic polymorphisms, such as the microsatellites in *AVPR1a* promoter (RS3), have been implicated in social behavior in mammals. In humans, there is a complex RS3 located in the 5' flanking region of *AVPR1a*, and at least 16 alleles were observed [13]. Previous studies demonstrated that RS3 is associated with human autism [14-16], sexual behavior [17, 18], altruism [19], maternal behaviors [20], and pair bonding in men [21]. Additionally, RS3 alleles in healthy humans are associated with increased activation of amygdale, an important area for pair bonding formation [22]. Recently, RS3 is associated with social personality in chimpanzee [23].

However, to our knowledge, there are no comprehensive data regarding RS3 variation in primates, and its relationship with one of important social behaviors, social monogamy, is also unclear. Therefore, all available published data of RS3 sequences in primates were collected and analyzed in this study.

Materials and Methods

Sequences

All available public RS3 sequences were collected from NCBI, UCSC Genome Browser, Ensembl, and literatures, which include a total of 24 individuals from 18 primate species.

Social monogamy definition

Social monogamy (not genetic monogamy) in mammals refers to a long term or sequential living arrangement between an adult male and an adult female. This arrangement is frequently defined as: sharing the same territory, obtaining food resources, and raising offspring together. The presence or absence of social monogamy in primates was based on recent surveys [24, 25].

Statistical analysis

Statistical significance of RS3 repeats between the social monogamous and non-social monogamous species were evaluated by ANOVA (in IBM SPSS Statistics 20, SPSS In., U.S.A). The significance level was set at $P < 0.05$.

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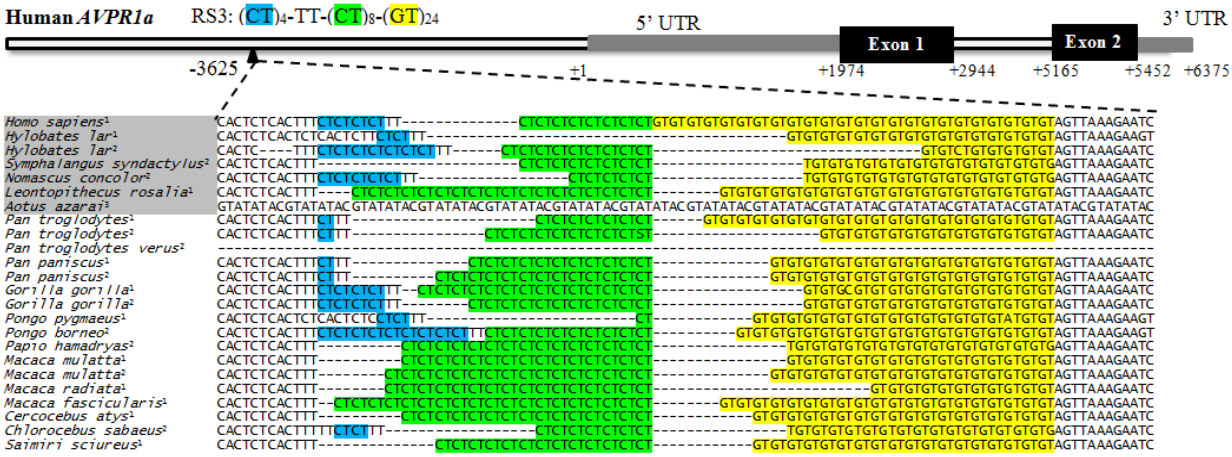

Figure 1: RS3 alignment in monogamous species (shaded) and non-monogamous species, with– indicating a gap; and 1, 2, 3 represent reference [26], reference [27] and reference [28], respectively.

Results

All publically available RS3 data were collected and aligned based on the three literatures [26-28]. A total of 24 animals were obtained in this alignment (Figure 1). Species *Aotus* did not show the RS3 alleles, which was replaced by microsatellite "GTATATAC". One of *Pan troglodytes* also did not show a RS3 region[27]. Of the CT_4 in RS3, other five variations were identified, including CT_0, CT_2, CT_5, CT_7 and CT_9. Other 11 and 8 types of $CT_8$and GT_{24}in RS3 were observed in these species (Figure 1). Although the microsatellites show marked variability in primates, no association was observed between RS3 alleles and social monogamy (P> 0.05). Attempts were made to amplify the RS3 regions of social monogamous species, like *Callithrix jacchus, Leontopithecus rosalia, and Callimico goeldii*. However these PCRs were unsuccessful.

Discussion

Among the primates, the regular expression of social monogamy is rare or absent in prosimian and Old World primate genera. In hominoid primates (apes and humans), social monogamy is noted in gibbons, siamangs and human, but not in other hominoid genera. In contrast, social monogamy is relatively prevalent in New World Monkeys (NWM), with 50% of genera routinely displaying this social system[24,25,29]. Since AVP and *AVPR1a* are implicated in social behavior [7-12,30,31], the aim of this study was to investigate whether genetic variability of RS3 in *AVPR1a* are associated with social monogamy in primates.

There is increasing evidence that RS3 of *AVPR1a* is associated with social behavior [13-23]. In this study, the RS3 region in some social monogamous species were attempted to be amplified and sequenced, but ultimately failed, which coincides with previous reports [28]. Therefore, in this study, all publically available RS3 data in primates were collected, aligned and analyzed, including six monogamous species and 12 non-monogamous species (24 animals; Figure 1). However, the polymorphic RS3 in this study did not demonstrate any association with social monogamy in primates (P> 0.05). Our findings agree with previous results that found no general association between RS3 polymorphisms and social behavior across part of primate tax [26,27]. Notably, RS3 is completely absent in monogamous Owl monkeys (*Aotusazarai*) [28]. A recent study also indicates the complex relationship between AVRP1a and social monogamy [32]. Whether RS3 is associated with social monogamy in primates needs to be investigated in future.

In conclusion, although RS3 genetic diversity was found in these primate species, no significant association was observed between RS3 and social monogamy in primates.

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