

**The 5-HT transporter gene-linked polymorphic region
(5-HTTLPR) in evolutionary perspective: alternative biallelic
variation in rhesus monkeys**

Rapid Communication

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Summary. By conferring allele-specific transcriptional activity on the 5-HT transporter gene promoter in humans, the 5-HT transporter gene-linked polymorphic region (5-HTTLPR) influences a constellation of personality traits related to anxiety and increases the risk for neurodevelopmental, neurodegenerative, and psychiatric disorders. Here we have analyzed the presence and variability of the 5-HTTLPR in several species of primates including humans, and other mammals. PCR, Southern blot, and sequence analyses of the 5-HT transporter gene's 5'-flanking region in different mammalian species confirmed the presence of the 5-HTTLPR in platyrrhini and catarrhini (hominoids, cercopithecoids) but not in prosimian primates and other mammals. Since the 5-HTTLPR is unique to humans and simian primates, a progenitor 5-HTTLPR sequence may have been introduced into the genome some 40 Mio. years ago. In humans the majority of alleles are composed of either 14 or 16 repeat elements, while alleles with 18 or 20 repeat elements are rare. In contrast, great apes including orang-utan, gorilla, and chimpanzee display a high prevalence of alleles with 18 and 20 repeat elements. In hominoids all alleles originate from variation at a single locus (polymorphic locus 1). In the 5-HTTLPR of rhesus monkeys (rh5-HTTLPR) we found an alternative locus for length variation (polymorphic locus 2) generated by a 21 bp insertion/deletion event. The existence of a distinct biallelic variation of the 5-HTTLPR in rhesus monkeys but similar allele and

genotype frequencies in this species and humans supports the notion that there may be a relationship between functional 5-HT transporter expression, anxiety-related traits, and the complexity of socialization in human and non-human primate populations.

Keywords: Serotonin transporter gene-linked polymorphic region, allelic variation, primates, macaca mulatta, evolution.

Introduction

Serotonin (5-HT), acting at multiple receptor subtypes, regulates physiological functions as diverse as mood, emotion, cognition, and motor functions as well as circadian and neuroendocrine rhythms including food intake, sleep and reproductive activity. By fine-tuning the magnitude and duration of postsynaptic receptor-mediated signalling, 5-HT transport into the presynaptic neuron plays a key role in the spatio-temporal regulation of 5-HT neurotransmission. Several therapeutics (e.g. antidepressant drugs), drugs of abuse (amphetamines, cocaine), and potent neurotoxins target this 5-HT transporter (5-HTT).

Functional promoter mapping revealed that transcriptional activity of the human 5-HTT gene (SLC6A4) is modulated by a polymorphic repetitive element (5-HTTLPR) (Heils et al., 1996). The 5-HTTLPR is located approximately 1 kb upstream of the 5-HTT gene's transcription initiation site and is composed of a variable number of repeat elements with the consensus sequence CCCCCCTGCACCCCCCAGCAT. The 5-HTTLPR is likely to form a complex secondary structure, silences transcriptional activity, contains positive regulatory elements, and confers allele-dependent differential transcriptional activity on the 5-HTT gene promoter.

Since allelic variation of the 5-HTTLPR is extensively used for association and linkage analyses of personality traits (Lesch et al., 1996) as well as of affective disorders (Collier et al., 1996), alcohol dependence (Sander et al., 1997), autism (Cook et al., 1997; Klauck et al., 1997), and late-onset dementias (Li et al., 1997), it may also be useful for inter-population and inter-species studies. In this paper, we analyze the presence and variability of the 5-HTTLPR in humans, in several species of non-human primates (e.g. chimpanzee, orang-utan, gorilla, and macaque), and other mammals (tree shrew, mouse).

Materials and methods

Blood or tissue for DNA isolation and analysis was obtained from the following species: *mus musculus* (n = 2), *tupaia belangeri* (n = 3), galagoids (prosimian primate: *galago demidovii* [n = 4]), platyrrhini (new world monkeys: *ateles geoffroyi* [n = 2], *callithrix jacchus* [n = 1]), catarrhini (old world monkeys: *papio anubis* [n = 1], *macaca mulatta* [n = 154]), hominoids (orang-utan: *pongo pygmaeus* [n = 1], gorilla: *gorilla gorilla* [n = 1], chimpanzee: *pan paniscus* [n = 1], *pan troglodytes* [n = 2]), and humans.

Heterologous (human) oligonucleotide primers flanking the 5-HTTLPR (sense, str5, 5'-GGCGTTGCCGCTCTGAATGC; antisense, str3, 5'-GAGGGACTGAGCTGGACAACCAC) were used in all species. In macaques 5-HTTLPR genotype frequency of the two allelic variants (long rh5-HTTLPR, rhL; short