# Predisposition to Impulsivity and Risk-taking: Dopamine D4 Receptor (DRD4) Polymorphic Gene Linked to "Novelty Seeking" Personality Trait

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**Abstract:**

Genetic variation may play a significant role in the expression of complex personality and psychological traits. This article examines the relationship between heritable biological mechanisms and the psychological trait, impulsivity. In particular, dopamine is proposed to play a role in impulsive behaviours, and numerous studies have implicated functional polymorphisms of dopamine-related genes in impulsivity. This article reviews several studies concerning the role of dopamine receptor (DRD4) polymorphisms in the expression of an impulsivity sub-trait known as "novelty seeking". Furthermore, this article focuses on recent approaches to the study of genetic variation, approaches to the measurement of novelty seeking, as well as other possible regulators of the trait in addition to genetics.

**Keywords:** Impulsivity; novelty-seeking; dopamine; DRD4; genetic polymorphisms

## Introduction

Impulsivity is a complex, psychological construct that appears in various forms and to different degrees in major systems of personality (Whiteside & Lynam, 2000, p. 669). Because of its multifaceted nature, impulsivity has been difficult to exclusively define and measure. Some major features include disinhibition and risk-taking, a tendency to act rapidly without forethought and complete planning, and acting to immediately satisfy a desire, without regard for possible consequences (Dickman, 1993, p. 151). Impulsivity is conceptualized on a continuum. This continuum is fairly subjective, as it can vary with the stimulus, situation, or individual. For example, "impulsive" individuals can be characterized by those who are outspoken and extroverted, to those who engage in thrill-seeking activities such as bungee jumping or rock climbing, to individuals who engage in inherently dangerous, high-risk behaviour substance abuse, aggression/violence, and reckless driving. Impulsivity has also been used as diagnostic criteria for psychiatric disorders as varied as kleptomania, borderline personality disorder, attention-deficit/hyperactivity disorder, mania, bulimia nervous, substance abuse/addiction, and paraphilias (Whiteside, Lynam, 2000, p. 669). There is evidence to support that genetics may play a role in one's susceptibility to this trait.

For the purpose of analyzing the degree of genetic predisposition in impulsivity, a sub-trait called "novelty seeking" will be used as an objective proxy measurement. This trait relates to the risk-taking aspect of impulsivity. Novelty seeking is defined a lack of planning and the tendency to act impulsively without thinking, as well as experience seeking, or the willingness to take risks for the sake of excitement or novel experiences (Zuckerman et al., 1993, p. 757). The Temperament Character Inventory is a psychometric instrument used to measure seven dimensions of personality traits. Individuals that score higher than average in the novelty-seeking quotient on the TCI tends to be impulsive, extravagant, fickle, quick-tempered, excitable, and exploratory (Cloninger et al., 1991, p. 1047).

A promising candidate gene for influencing the complex personality trait of novelty seeking is the dopamine receptor (DRD4) gene. Research demonstrates that polymorphisms in this gene are associated with variation in novelty seeking and exploratory behaviour in a range of species, including humans.

Measurement of Novelty Seeking in Research Studies

A variety of behavioural methods can be used to evaluate novelty-seeking. These include particular punished/extinction paradigms, reward-choice paradigms, and response disinhibition/attentional paradigms. For example, one study examined the relationship between the DRD4 dopamine receptor gene and novelty seeking in primates. Novelty seeking was measured by the latency to approach a large, potentially threatening novel object placed in the home enclosure (Bailey, Breidenthal, Jorgensen, McCracken, & Fairbanks, 2007, p. 23). Another notable study examined the same association in a wild bird called the great tit. Assessment of great tit personality took place in a testing arena, where the hops and flights between perches on artificial trees were used as a proxy for exploratory behaviour (Bensch & Tschirren, 2010, p. 624). A third study used a place-conditioning method where rats received access to novel objects repeatedly in one environment then spent an equal amount of time in a second environment without exposure to novelty. In subsequent choice testing, it was determined that rats had preference for the environment paired with novelty, indicating that novel stimuli have a rewarding quality (Bevins, 2001, p. 190).

Behavioural measures to study novelty seeking are most commonly used on animal models. The methodology for human studies, on the other hand, usually involves employment of psychometric instruments and personality inventories to measure the novelty seeking trait. Most notably, the Temperament Character Inventory (Cloninger et al., 1991, p. 1047), the Sensation Seeking Scale (Zuckerman, et al., 1993, p. 758), and the NEO Personality Inventory (NEO-PI-R) (Costa & McCrae, 1992) are used. Seminal work in this field by Robert Cloninger used the TCI, to determine research participants' degree of novelty-seeking behaviour patterns. This self-report questionnaire measured four separate domains of personality (novelty-seeking, harm avoidance, reward dependence, and persistence) that are each hypothesized to have distinct genetic and neurochemical bases. Participants are asked to answer 240 questions, among them queries like, "I like to experience new things for the simple enjoyment or thrill of it, even if most people think this is a waste of time," or "It is hard for me to stay interested in the same things for a long time because my attention often gets distracted by other things," and "I would enjoy the sensation of skiing very fast down a high mountain slope" (Cloninger et al., 1991). Quantitatively measuring participants' novelty seeking behaviour patterns allowed researchers to correlate them with certain characteristics of a polymorphic gene coding for a dopamine receptor protein (DRD4).

Biological Pathways Linked to Novelty Seeking and Relevant Studies

Findings from numerous studies suggest that individual degrees of the impulsivity, risk taking, and the novelty seeking trait are linked to genetic variability in the transmission of the neurotransmitter, dopamine. The dopaminergic system has been strongly linked to the reward system of the brain. This neurotransmitter is released in key brain areas in response to natural and primary rewards such as food, drink, and sex, and has been associated with feelings of gratification and reinforcement (Iverson & Iverson, 2007, p. 188). A study done on rats showed that, along with natural rewards, novel stimuli are a determinant of the responsiveness to dopamine in the midbrain. Rats in a non-deprived state that were fed novel, palatable food, elicited a more immediate increase in extracellular dopamine release in the nucleus accumbens than rats given their standard food. These results implicate that novelty is important for activation of mesolimbic dopamine, and that dopamine signals adapt to the repeated presentation of reward (Spanagel & Weiss, 1999, p. 526).

More recently, a link between genetics and the novelty seeking trait has been put forth. A group of researchers at the Herzog Memorial Hospital in Jerusalem and Ben-Gurion University in Israel have shown that novelty seeking is associated to a particular polymorphism of the D4 dopamine receptor (DRD4) gene. The DRD4 gene, found on chromosome 11p15.5, codes for the dopamine receptor D4, which is a G-protein coupled receptor. DRD4 is a D2-like receptor which, when activated, causes inhibition of adenylyl cyclase, thereby reducing intracellular concentration of the second messenger cyclic AMP (Neve, Seamans, & Trantham-Davidson, 2004, p. 165). The Herzog-BenGurion study showed that, among 124 unrelated participants, higher than average TCI novelty seeking scores were significantly associated with an exonic polymorphism, the 7-repeat allele at the locus for DRD4 (Ebstein, 1996, p. 78). The participants donated blood samples, and DNA was isolated using the polymerase chain reaction (PCR) and electrophoresis to measure the exon of the DRD4 gene. These results were corroborated by Benjamin et al. (1996) at the National Institute of Health in Maryland, United States, who studied the relationship between DRD4 exon III sequence variants and NEO-PI-R test scores in a population of 315 mostly male siblings, other family members, and unrelated individuals. In addition to confirming Epstein's results, this study showed that the association is the result of genetic transmission, rather than population stratification (p.84). Not only did the two groups find the same correlation between exon repeat length and novelty seeking using different personality questionnaires, but they found it among different ethnic groups of both sexes, and within family members and unrelated individuals (Ebstein, 1996, p. 80).

A study on the molecular characterization of the DRD4 gene, in both humans and rats, has revealed its highly polymorphic 16-amino acid repeat region in the putative third cytoplasmic loop (Asgari, et al., 2004, p. 364). There is a 48-base pair variable number tandem repeat in exon III which ranges from 2 to 16 repeats. The 7-repeat allele is considered the 'DRD4 long' variant, which results in transcription of a longer receptor protein. Differences in ligand binding have been observed between the most common short receptor (4 repeats) and the long variant (Asgari, et al., 2004, p. 364). This study also shows that the outsized D4 receptor protein has decreased functional ability to bind dopamine. In relation to novelty seeking and impulsivity, it is hypothesized that because of low basal dopaminergic activity and resulting low activity of this natural reward pathway, individuals with this variation of the DRD4 gene are susceptible to compensatory reward-seeking behaviours (such as impulsive action toward novel stimuli, food, sex, and drugs) (Cloninger, 1986, p. 167). Numerous additional studies supporting the hypothesized link between DRD4 gene and novelty seeking should be noted. They include studies showing that the number of exon III repeats affects the binding of ligands to the receptor; that DRD4 is distributed in the prefrontal cortex and limbic areas involving cognition, emotions, and decision-making; that dopamine mediates exploratory behaviour in experimental animals; that the rewarding effects of ampehtamines and cocaine are related to dopamine release; and that novelty seeking scores are low in dopamine-deficient Parkinson's disease patients (Benjamin et al., 1996, p. 84).

## Conclusion

It is said that "allelic association studies are the strategy of choice for detecting quantitative trait loci, such as those involved in personality, as they provide the statistical power needed to detect relatively small gene effects that contribute to complex behavioural traits" (Ebstein, 1996, p.80). Epstein's and Benjamin's allelic studies have functional significance in determining a partial genetic link to

the novelty seeking trait. Both groups concluded its correlation with DRD4 exon III repeat length, which seems to have an impact on the ability of dopamine to bind to its D4 receptors. Epstein reports that the repeat sequence may confer other properties to the D4 receptor protein that are undetected in binding studies, and that further investigation of the effects of the polymorphism on receptor activities would be valuable.

Although these studies are informative, the DRD4 gene does not entirely explain the biological basis for novelty seeking. Animal models and twin studies have indicated that about half of novelty seeking behaviour is attributable to genes, while the other half to environmental conditions (Ebstein, 1996, p. 80). Epstein acknowledges that there are probably four or five other genes involved in expression of the trait with the same influence as the D4 receptor, and that DRD4 probably accounts for 10% of the difference in novelty seeking behaviour between individuals.

One must consider other factors that contribute to regulation of this trait, including other associated genes and neurochemical pathways, environmental circumstances, and psychopathological disorders. There is research indicating a possible overlap in the neurobiological processes involved in novelty seeking. Neuroanatomical areas that are involved in dopaminergic activity include the nucleus accumbens, hypothalamus, amygdale, hippocampus, and frontal cortex, and thus study of these systems and their link to novelty seeking should be explored. Additionally, consideration should be given to other neurotransmitters that are involved in reward pathways such as serotonin, acetylcholine, and norepinephrine.

Furthermore, it is important to note that novelty seeking only measures one aspect of impulsivity. Perhaps studies done on the DRD4 gene in relation to other subtraits or risk factors for impulsivity, such as addiction or aggression, could enhance this biological evidence for impulsivity.

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