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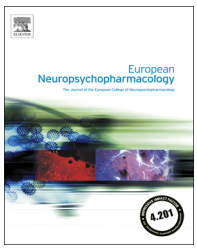

Autism, DRD3 and repetitive and stereotyped behavior, an overview of the current knowledge

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Abstract
The SNP rs167771 of the dopamine-3-receptor gene (DRD3) has been associated with autism spectrum disorder (ASD) in samples from the United Kingdom, The Netherlands and Spain. The DRD3 polymorphisms of rs167771 are significantly associated with a specific type of repetitive and stereotyped behavior, called sameness. Repetitive and stereotyped behavior occurs in several neuropsychiatric disorders and the combined picture across these disorders strongly suggests the involvement of the basal ganglia - frontal lobe circuitry. In autism, abnormalities of the basal ganglia, in particular the caudate nucleus, are the best replicated findings in neuroimaging studies. Interestingly, the DRD3 gene is highly expressed in the basal ganglia, most notably the caudate nucleus. The rs167771 SNP was recently also found to be related to risperidone-induced extra-pyramidal side effects (EPS) in patients with autism, which is important since risperidone is approved for the treatment of aggression, irritability and rigid behavior in ASD. To conclude, striatum abnormalities in autism are associated with repetitive and stereotyped behavior in autism and may be related to DRD3 polymorphisms.

1. Autism spectrum disorders (ASD)

Humans have a rich social life. They have a set of unique skills to interact with other people, understand the meaning of other people's actions and emotions, communicate through complex language, collaborate in order to plan future events, and switch rapidly between different strategies to adapt to the environment. There is huge normal variation between people in how often, how successful and in which way they apply these skills. However, some people typically already early in life present with severe and persistent impairments of these skills. When this falls outside normal variation, these people will be diagnosed as having Autism Spectrum Disorder

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(ASD), or shortly, autism. The clinical signs of autism in general present during infancy or early childhood and have a highly variable course and outcome. Some patients only develop mild symptoms with spared language skills. Others suffer from severe symptoms often accompanied by intellectual disability and epilepsy. Some 5% of individuals with autism show unusual abilities, ranging from splinter skills such as the memorization of trivia to the extraordinarily rare talents of prodigious autistic savants. Many individuals with autism show superior skills in perception and attention, relative to the general population. Sensory abnormalities are almost always present and include under-responsivity (for example, not reacting at all to loud sounds) and over-responsivity (for example, distress from noises due to planes in the air that normal people would not even notice). About 60–80% of people with autism have motor abnormalities including hypotonia, poor motor planning, poor coordination, and toe walking. Patients with autism have also increased rates of somatic diseases, such as problems of the digestive tract, overweight and immunological abnormalities. With the exception of a few cases, autism is a lifetime persistent disorder. Indeed, autism may have negative impacts on health, wellbeing, social integration and quality of life of individuals and families. Long-term follow-up studies have found above-average mortality rates compared to age- and sex-matched controls. It is estimated that one in every 110 children is diagnosed with autism, making it more common than childhood cancer, juvenile diabetes and pediatric AIDS combined. Boys are diagnosed with autism three to four time more often than girls. The prevalence of autism has substantially increased over the last decades. This increase is poorly understood, but broader diagnostic criteria, improved recognition and diagnosis, and environmental influences are reasons often considered. Autism is a group of heterogeneous disorders that have a large number of symptoms in common. These symptoms are grouped in three domains: (1) abnormal social interaction, (2) abnormal verbal and nonverbal communication and (3) stereotyped and rigid patterns on behavior and interests.

2. Genetic factors in autism and DRD3

Genetic factors are the most significant contributors to the etiology of autism. With heritability estimated to be about 80% or more, the genetic contribution of autism is one of the highest observed for any common disorder. The genetic architecture of autism, however is complex. While initially "common variants" were thought to play a major role it has become clear that other forms of genetic variation are at least equally important. It is now generally accepted that moderate to strong risk variants such as de novo copy number variants (CNVs) are an important contributor to the disease risk. In the majority of people with autism, no identifiable genetic cause or genomic risk factor is identified. This means that the majority of risk variants will be of moderate effect size. With respect to DRD3, the combined findings of chromosomal studies and association studies strongly suggest a role for DRD3 in autism. Chromosomal microarray analysis studies provide some circumstantial evidence for DRD3 involvement in autism. Two studies describe an increased risk for ASD in patients with “de novo” deletions of 3q13.2-q13.31 (see Table 1). It should be noted that the 3q13.2-q13.31 region is still relatively large and contains other important genes as well. Interestingly, deletions of this region appear also to be accompanied by motor abnormalities (Shuvarikov, et al., 2013; Wiśniowiecka-Kowalnik, et al., 2013). Bearing the complex genetics of autism in mind, it is remarkable that recently in samples from The Netherlands, the United Kingdom (de Krom, et al., 2009) and Spain (Toma, et al., 2013) the SNP rs167771 of the dopamine-3-receptor gene (DRD3) has been associated with ASD. With respect to the study of DRD3 in samples from the United Kingdom (UK) and the Netherlands, data of both samples were combined in a joint statistical analysis. A significant association between SNP rs167771 located in the DRD3 gene was found, which survived statistical correction for multiple testing. It is important to note, that this study was designed to investigate possible genetic overlap between ADHD and ASD. For this reason 1536 single nucleotide polymorphisms (SNPs) covering candidate genes for ASD and ADHD were tested. Only SNPs with $p<0.01$ in the Dutch ADHD sample and a Dutch ASD samples were tested for association in the UK samples. DRD3 was included as candidate gene based on previous studies suggesting association with ADHD. As it turned out, DRD3 was associated with ASD, but not ADHD.

The same SNP (rs167771) was later tested in a Spanish sample (Toma, et al., 2013) and again significant association between ASD and rs167771 was observed. Samples sizes were relatively small however, with a combined number of

Table 1 Autism, DRD3 and genetic findings.

	Subjects	Findings
Chromosomal microarray analysis studies		
Shuvarikov et al. (2013)	9 subjects with de novo deletions of 3q13.2- q13.31	Autism spectrum disorders in 3/9 subjects
Wiśniowiecka-Kowalnik et al. (2013)	145 ASD patients included one patient with de novo del3q13.2q13.31	3q13.2q13.31 patient presented Atypical autism
SNP association studies		
Toma et al. (2013)	326 autistic patients 350 controls	rs167771 (DRD3) associated with ASD
Staal et al. (2012)	91 ASD patients with rs167771 genotype AA 66% AG 29% GG 5%.	AA variant rs167771 associated with increased sameness
De Krom et al. (2009)	144 ASD patients (Dutch) 404 controls (Dutch) 128 ASD patients (UK) 124 controls (UK)	rs167771 (DRD3) associated with ASD