

## Short report

# DRD3 gene and striatum in autism spectrum disorder

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**Summary**

A single-nucleotide polymorphism (SNP) of the *DRD3* gene (rs167771) was recently associated with autism spectrum disorders (ASD). Different polymorphisms of rs167771 corresponded to varying degrees of stereotyped behaviour. As DRD3 receptors are relatively overexpressed in the striatum, we investigated whether striatal volume was related to these polymorphisms in autism. We assessed volumes of caudate nucleus and putamen in 86 participants with ASD (mean age 15.3 years). MANCOVA showed an association between alleles of the rs167771 SNP and

the volume of striatal structures. Furthermore, greater caudate nucleus volume correlated with stereotyped behaviour. These findings support a relationship between *DRD3* gene SNPs, striatum and stereotyped behaviour in ASD.

**Declaration of interest**

None.

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Autism spectrum disorders (ASD) are neurodevelopmental disorders that are marked by deficits in social interactions, communication, and stereotyped and repetitive behaviour. The third cluster of symptoms is often severely impairing, and the fixed routines, rituals and repetitive activities cause much suffering for affected individuals. Furthermore, they often cause severe loss of functioning and these behaviours are one of the main reasons for pharmacological interventions in children with ASD. Managing interactions with individuals who experience these symptoms is often challenging for clinicians and for caregivers. The neurobiology underlying these symptoms is not well understood. There is some evidence that repetitive behaviour is related to changes in fronto-striatal circuits,<sup>1</sup> and this relationship appears quite marked in ASD.<sup>2,3</sup> Recently, we reported that a specific type of repetitive behaviour ‘insistence on sameness’, a factor derived from the Autism Diagnostic Interview (ADI),<sup>4</sup> is associated with polymorphisms of single-nucleotide polymorphism (SNP) rs167771 of the dopamine-3-receptor gene (*DRD3*) in ASD.<sup>5</sup> This is of interest for several reasons. First, polymorphisms of rs167771 have now been associated with ASD in British, Dutch and Spanish samples.<sup>6,7</sup> Second, *DRD3* is relatively overexpressed in the striatum, including the caudate, which in turn is affected in ASD.<sup>8</sup> Third, the rs167771 SNP was recently related to extrapyramidal symptoms (EPS) induced by risperidone.<sup>9</sup> Risperidone is frequently administered for the treatment of stereotyped behaviour in ASD. In sum, from these studies there seems to be a relationship between rs167771, striatum and repetitive and stereotyped symptoms in ASD. To make neurobiological findings relevant for daily clinical practice it is pivotal to understand the relationship between genetic risk factors, on the one hand, and brain changes and symptoms on the other. Given the suggestive but inconclusive evidence of a relationship between polymorphisms of *DRD3*, striatum and stereotyped and repetitive behaviour, we set out to investigate whether polymorphisms of the rs167771 SNP were related to striatal volume and stereotyped behaviour in ASD.

**Method**

The volumes of striatum (caudate, putamen) and the whole brain were measured on anatomical magnetic resonance imaging (MRI) scans from 86 participants with ASD. Prior to inclusion, written informed consent was obtained from the participants and their

parents and the study was approved by the ethics committee of the UMC Utrecht, The Netherlands. All participants met the DSM-IV(TR) criteria for ASD.<sup>9</sup> Clinical assessment was based on multidisciplinary evaluation and included the Autism Diagnostic Interview-Revised (ADI-R)<sup>10</sup> and the Autism Diagnostic Observation Schedule (ADOS).<sup>11</sup> MRI scans were acquired on a 1.5-T scanner (Philips, Best, The Netherlands).  $T_1$ -weighted three-dimensional (3-D) fast-field echo scans with 1.2 mm and  $T_2$ -weighted dual echo turbo spin echo scans with 1.6 mm contiguous coronal slices of the whole head were acquired. Freesurfer-based automatic structural segmentation, followed by visual inspection and correction if necessary was used for volume measurement of the whole brain, intracranial volume and striatum. The reliability of this method is well established (for example Dewey *et al*<sup>12</sup>), and online Fig. DS1 shows examples of segmentation. All images were coded to ensure raters were masked to participant identity and diagnosis.

**Results**

The mean age of participants was 15.3 years (s.d. = 4.5 years, range 6.8–30.5 years), and mean IQ was 103 (s.d. = 17.9, range 55–152). The frequency distribution of the rs167771 SNP was: homozygote AA 66% ( $n = 57$ ), heterozygote AG 29% ( $n = 25$ ), homozygote GG 5% ( $n = 4$ ). Because of the small number of individuals carrying two copies of the GG allele, the GG and AG groups were combined into one group of G-allele carriers. All volume measures showed a normal distribution in the two groups. There were no laterality effects. MANCOVA, with age as a covariate, showed a significant association between the type of allele and total striatum volume ( $F = 3.055$ , d.f. = 4,  $P = 0.022$ ). This effect was not specifically related to caudate nucleus or putamen volume. Further analysis showed that this effect was as a result of a difference in laterisation of the striatum between the groups. The left/right ratio in the AA group was 1.036, in the G-allele group it was 1.010 ( $F = 8.232$ , d.f. = 1,  $P = 0.005$ ). Whole brain volume did not differ between groups. In a follow-up analysis, greater caudate nucleus volume was correlated with higher-order stereotyped behaviour ( $R = 0.278$ ,  $P = 0.040$ ), but not other symptom clusters or global functioning. Higher-order repetitive behaviour is a subset of ADI-R items related to insistence on sameness. It encompasses behaviour such as preoccupation with one subject or activity and strong attachment to one specific object.

## Discussion

The central finding of this study is that polymorphisms of an SNP in the *DRD3* gene (rs167771), striatal volume and stereotyped behaviour are related in ASD. As such, our data support the notion that there may be genetically determined subgroups within the ASD spectrum, associated with differing behavioural phenotypes. Combining genetic and neuroimaging research to further understand the interplay between neural mechanisms and genetic variants has been applied with some success in other psychiatric disorders, such as schizophrenia.<sup>13</sup> To date, in ASD, there have been no reports of a direct link between a genetic risk factor, brain structure and specific symptoms. Given the complexity of the genetics of ASD, the present study suggests one direction for research toward unravelling this complex and heterogeneous disorder.

From a clinical perspective our findings combined with recent findings from pharmacological studies may eventually have pharmacological implications, given that the rs167771 SNP was recently also associated with EPS.<sup>9</sup>

Although the number of participants in this study is relatively high for neuroimaging studies in ASD, it is relatively small for genetic studies. Therefore, we chose to test a single *a priori* hypothesis based on evidence from genetic and neuroimaging studies. As such, we did not have as many comparisons as less constrained imaging genetics studies and did not need to apply the same stringent correction for multiple comparisons. This was a crucial factor in being able to detect the subtle effect in this study.

Our findings underscore that genetic risk factors in ASD may relate to specific types of symptoms, rather than to the whole behavioural spectrum and that this may be mediated through specific brain networks. Genetic fractionation of autistic traits has been shown previously and appears to also be present in the general population.<sup>14</sup> This suggests that the relationship between rs167771 polymorphisms, striatum and stereotyped behaviour may in fact represent a more general mechanism present across the boundaries between disorders. As this is the first study to show a direct relationship between a common genetic variant, brain structure and specific symptoms in ASD, caution in interpretation is essential. Provided our findings are replicated, new studies may address potential pharmacological implications and to what degree these changes are specific to autism.

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