Case Report

Heterozygous Deletion of Macro Domain Containing 2 (MACROD2) is Associated with Autism Spectrum Disorder

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Autism Spectrum Disorder (ASD) is associated with genetic abnormalities in many cases, including common genetic syndromes, copy number variations, and rare genetic mutations. Studies have associated the 20p12.1 region and the Macro Domain Containing 2 (MACROD2) gene with ASD but this region or gene has not been specifically reported in an ASD case. In this case report we describe a non-syndromic boy with mild-to-moderate ASD who was found to have a deletion in the 20p12.1 region affecting only the MACROD2 gene. Other causes of ASD, including neurologic, metabolic and nutritional disorders, could not be identified. Given that this gene has been shown to be expressed in the ventricular zone of the brain during embryonic development, is associated with several neurologic and psychiatric disorders and has several associations with ASD, it may be an excellent candidate gene for non-syndromic ASD.
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INTRODUCTION

Autism spectrum disorder (ASD) refers to a group of neurodevelopmental disorders defined by social-communication deficits along with restricted and repetitive behaviors. Currently, the Centers for Disease Control estimate that 1 in 68 children in the United States are affected by an ASD.[1] However, the etiology of ASD is still poorly understood.[2] Studies suggest that both environmental and genetic components contribute to the etiology of ASD.[3,4] Several different types of genetic abnormalities appear to be related to ASD. While well-defined copy number variations appear to affect about 10% of children with ASD, other relatively common genetic syndrome, such as Fragile X, may account for another 5%-10%.[5] With the increased use of next-generation sequencing techniques, rare variations in specific genes have also been identified. As more genetic associations with ASD are discovered, a greater understanding of the causes of ASD will arise.

One gene that is of interest in relation to ASD is the Macro Domain Containing 2 (MACROD2) gene. Genes within the macro family have important roles in the regulation of gene expression and MACROD2 is highly expressed in the ventricular zone of the brain during embryonic development. Several studies have preliminarily linked this gene to ASD. A transgenerational case-control genome-wide screening study of 735 mother-child pairs identified the MACROD2 region as a candidate region for ASD[6] and MACROD2 is involved in a regulatory network suspected to be dysregulated in ASD.[7] While these studies suggest that the MACROD2 gene may be associated with ASD, they do not specifically implicate this gene as causative towards the development of ASD.

More extensive studies have examined a specific single nucleotide polymorphism (SNP) in MACROD2 in relation to ASD. In a study of 1,389 American and European families with 1,385 ASD probands, 1 million SNPs were analyzed for an association with ASD. The rs4141463 polymorphism in the MACROD2 gene was found to be over-transmitted in ASD.[8] However, in a follow-up study with 1,170 ASD cases and non-related ethnically matched controls, this relationship could not be confirmed.[9] This lack of specificity for ASD could be due to the fact that this gene is associated with ASD like traits within the general population. Indeed, in a study of 985 individuals from the general population that examined the association between a quantitative measure of autistic-like traits, the Autism Spectrum Quotient, and 5 SNPs, including the rs4141463 SNP in the MACROD2 gene, the MACROD2 SNP was found to be significantly associated with Communication/Mindreading subscale of the Autism Spectrum Quotient scale suggesting that it has a relation to ASD features in the general population.[10] Thus, these data suggest that a common variation in this gene is associated with ASD traits but do not provide insight into whether

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significant dysfunction in this gene, as may occur if at least one-copy is deleted, would result in a more severe phenotype that might result in the complete ASD phenotype.

Despite evidence that MACROD2 may be associated with ASD and ASD features, to the best of our knowledge, a case of a child with ASD in which the MACROD2 gene is specifically affected has not been documented. Demonstrating a severe disruption in the MACROD2 gene in a child with ASD without another explanation for ASD would suggest that the MACROD2 gene may have a causative role in the development of ASD. Here we present a case in which a child with ASD demonstrated a chromosomal deletion that only affected the MACROD2 gene. Workup for other causes of ASD did not reveal any other known causes for his ASD.

CASE REPORT

Pregnancy and birth was unremarkable. Family history was negative for developmental delays or neurological disorders.

The boy was diagnosed with speech and fine motor delay at 15 months. At 16 months old, repetitive behaviors began, leading to the diagnosis of ASD at 4 years of age. His development continued slowly with regular speech and occupational therapy. From kindergarten he remained in inclusion classes with resource room and special education support.

The child had a history of 10 seconds staring episodes, leading to a routine EEG and brain MRI that were unremarkable. At 10 years of age he developed episodic severe abdominal pain of unknown etiology despite recurrent gastrointestinal workups.

He has multiple biomedical treatments, most of which were of no particular help, including, methylcobalamin injections, hyperbaric oxygen therapy and gluten-free, casein-free diet.

At 12 years of age his growth was normal [Weight 25%ile; Height 50%ile; Body Mass Index 16%ile; Head circumference 50%ile]. General examination demonstrated no clear dysmorphology. Neurological examination demonstrated mild appendicular hypertonia and slightly reduced but symmetric deep tendon reflexes in upper and lower extremities. His language was very scripted but demonstrated adequate communication skills so that in superficial conversation his language and communication deficits might not be obvious.

Table 1 provides indices of ASD characteristics using validated ASD scales, including the Social Responsiveness Scale,[11] Aberrant Behavior Checklist[12] and Autism Symptoms Questionnaire.[13] The Social Responsiveness Scale suggests that this boy has mild to moderate ASD features. The Aberrant Behavior Checklist suggests only behavioral issues with mild to moderate hyperactivity. The Autism Symptoms Questionnaire endorses symptoms within all core domains of ASD.

A microarray consisting of 2.7M oligonucleotide probes, including ~2.0M unique non-polymorphic probes and ~700k SNP probes demonstrated a 633kb deletion in chromosome 20p12.1 which included only the MACROD2 gene. Extensive metabolic and nutritional testing demonstrated no identifiable metabolic or nutritional disorder.

Table 1. Standardized Autistic Characteristics Scales.

Social Responsiveness Scale (T-Score)	**Aberrant Behavior Checklist (Raw Score)**	**Autism Symptoms Questionnaire (Raw Score)**
Awareness: 64, Mild	Irritability: 6, Minimal	Social: 3
Cognition: 68, Moderate	Lethargy: 2, Minimal	Communicate: 4
Communication: 73, Moderate	Stereotypy: 0, None	Stereotypy: 3
Motivation: 60, Mild	Hyperactivity: 14, Moderate	Total: 10
Mannerisms: 64, Mild	Speech: 6, Moderate	Dx – Autism
Total: 69, Moderate ASD		
DSM-5 Compatible Scales		
Social Communication: 70, Moderate		
Repetitive/ Restricted Behavior: 64, Mild		

DISCUSSION

This, to our knowledge, is the first case report of a child with ASD and a chromosomal deletion involving the MACROD2 gene. This boy was symptomatic from early in life with slow progression in development with standard educational therapy. His development at 12 years of age was consistent with mild to moderate autism and he had relatively little aberrant behaviors. His physical and neurological examinations were not evident of a distinctive from of idiopathic ASD, suggesting he should probably be considered non-syndromic.

A case of Kabuki syndrome has been reported with a microdeletion in exon 5 of MACROD2.[14] The case reported herein demonstrated none of the classic characteristics of Kabuki syndrome such as growth retardation, facial dysmorphology reminiscent of Japanese Kabuki theater,

congenital malformations of the heart, kidneys or vertebra, and/or seizures. This could suggest that in the Kabuki case, other, unidentified gene abnormalities may also have been involved.

The MACROD2 has also been implemented in other neurological disorders such as Alzheimer's Disease,[15] stroke[16] and multiple sclerosis,[17] neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder,[18] and psychiatric disorders such as Schizophrenia.[19] Thus, abnormalities in this gene many have wide spread implications for neurological and psychiatric disease. The fact that MACROD2 is implicated in a wide range of neurological and psychiatric disorders may suggest that abnormalities in the MACROD2 gene act in concert with other genetic abnormalities to result in the particular phenotypic expression of neurologic and psychiatric disease.

Further cases and examples of individuals with ASD and other neurological and psychiatric disorders that manifest abnormalities in the MACROD2, including SNPs, may be helpful to further delineate the significance of this gene in disorders of the brain.

CONFLICT OF INTEREST
The author has no conflicts of interest to declare.

FINANCIAL DISCLOSURES
The author has no financial disclosures to declare.

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