Getting to the bottom of autism spectrum and related disorders: MBD5 as a key contributor

References


Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder

Talkowski et al. (2011)
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Autism spectrum disorder (ASD) and related neurodevelopmental conditions are complex disabilities characterized by intellectual delay, language and motor impairment (1). In recent years, the genetic underpinnings of such disorders have begun to be revealed with the advances in genomic microarray technology and similar tools. In many cases, structural variations such as microdeletions are key genetic contributors, often comprising of single genes that give rise to a specific microdeletion phenotype. The 2q23.1 microdeletion is one that has been implicated in conditions spanning a variety of features with overlapping phenotype (2) but specific genes responsible for generating the observed phenotype have not yet been identified.

Talkowski et al. began by establishing an international collaboration in order to assemble a cohort of individuals possessing a structural variant found in the 2q23.1 region. Following alignment of the structural rearrangements from 65 individuals, the region with the smallest overlap was found to contain only a single gene, MBD5, which was commonly disrupted in all samples in both coding and non-coding regions. By taking advantage of the large cohort size and accompanying clinical information, the authors examined the individual phenotypes across a cohort of individuals with MBD5-specific deletions as well as in a cohort consisting of a broader 2q23.1 deletion, and found that greater than 80% of neurological and neurobehavioral features in the deletion syndrome coincide with phenotypic features found in individuals with MBD5-specific deletions (1). Disruptions in the MBD5 gene included intragenic non-coding deletions between exon 1 and the coding sequence start site, as well as several translocations within the coding region. Despite the overlap in phenotype between the microdeletion group and those with MBD5-specific mutations, however, the authors did note differences between the groups, including various craniofacial manifestations that are more frequently present in the deletion group. MBD5 mRNA expression was also shown to be significantly reduced, suggesting it is haploinsufficient and appears to be highly penetrant given the lack of MBD5 deletions in a large control cohort. Furthermore, high penetrance was suspected given the observation that partial or complete deletion of the MBD5 region consistently resulted in the observed phenotype. Sequencing of the MBD5 gene revealed a p79Gly>Glu missense mutation in a critical
and highly conserved methyl-binding domain that was overrepresented above other variants within the study group. The minor allele frequency for this variant was found to be significantly higher in ASD subjects, suggesting a potential increased risk to ASD individuals conferred by the mutation.

*MBD5* is a gene encoding for a highly conserved methyl-CpG-binding domain. As its name implies, this domain is thought to facilitate the binding of DNA at methylated CpG islands. Though the exact mechanism of DNA binding has not yet been elucidated, recent data suggests that it may play a key role in the regulation of gene expression through the formation of heterochromatin (3).

Two other related genes, *MECP2* and *MEF2C*, have been implicated in Rett syndrome and in a 5q14.3 microdeletion with an ASD phenotype, respectively. *MECP2* also encodes for a methyl-CpG-binding domain and the authors suggest that its role as the causative locus in Rett syndrome (a neurodevelopmental condition) further points to the likelihood of *MBD5* being the causative gene in 2q23.1 microdeletion syndrome. *MEF2C*, a gene involved in development, neurogenesis and neuronal gene regulation, has been shown to interact with *MBD5* in a complex that binds DNA (Fig. 1), and given its association with an ASD phenotype consisting of similar clinical features, it is reasonable to predict that the two genes could be involved in a common pathway which regulates the expression of key neurodevelopmental genes through epigenetic mechanisms. Further work will be needed to directly assess the functional implications and behavioral phenotype of disrupted *MBD5* expression in an experimental model, so as to elucidate possible therapeutic targets.

As further data implicating genes involved in regulating DNA methylation and chromatin remodeling in neurodevelopmental disorders such as autism continues to emerge, it is evident that epigenetic modifications can play a significant role in the regulation of genes involved in neurogenesis and neural development. This work adds to an already large body of evidence suggesting that epigenetic deregulation as a result of chromosomal aberrations is one of the critical contributors to the manifestation of intellectual disorders such as ASD.