Diagnosis Advancements

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Critical review

Epigenetics and autism: Insights for future research

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Abstract

Introduction

Autism is approaching the numbers of an epidemic. Past efforts have focused on identifying the genetic basis of Autism Spectrum disorders with minimal success. Recently, a lot of work is being carried out in Epigenetics, Nutrigenetics in order to analyse the cause of Autism Spectrum Disorders. The present paper reviews the various studies being conducted in this domain and provides recommendations for further studies in this area.

Conclusion

As DNA methylation marks are reversible and dynamic, there is a possibility of reversing these marks by dietary intake of methyl donors and pharmacological agents which can therefore help in diagnosis and eventual treatment of autism.

Introduction

Autism (autism spectrum disorders) is a complex, strongly genetically influenced, and behaviourally defined disorder of the immature brain associated with very uneven intellectual abilities. Its many causes, robust heritability with epigenetic influences and a wide range of severity means that there is no symptom, no pathology, imaging, electroencephalography, or other biologic feature, and no biologic treatment that is universal or diagnostic of this developmental syndrome. Autism is approaching the numbers of an epidemic. The figures are staggering in the 1960s; four in 10,000 children have had autism. Today, according to Autism Speaks, an organization dedicated to facilitating global research into the causes, treatments and an eventual cure for autism, one in every 110 children is diagnosed with autism, making it more common than childhood cancer, juvenile diabetes and paediatric AIDS combined. U.S. government statistics suggest that the prevalence rate of autism is increasing 10-17% annually (Autism Society estimate based on 2003 US state educational data).

Past efforts have focused on identifying the genetic basis of Autism Spectrum disorders with minimal success. Recently, a lot of work is being carried out in Epigenetics, Nutrigenetics in order to analyse the cause of Autism Spectrum Disorders. The present paper reviews the various studies being conducted in this domain and will provide recommendations for further studies in this area.

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Discussion

Genetic and Epigenetic basis of Autism

Autism demonstrates robust heritability suggesting a strong genetic component. However, calculations of genetic heritability are based on a large extent on monozygotic twin studies. Monozygotic twins share not only genes but also environments and a common germ line DNA methylation pattern[1]. It is therefore possible that the genetic contribution to autism has been overestimated and the epigenetic component underestimated. Several studies point to an epigenetic basis for autism. RETT syndrome, a mental retardation disorder that is similar in certain aspects with autistic spectrum disorders, is caused by a deficiency in MeCP2, an epigenetic protein that binds methylated DNA and has several roles in interpretation of the DNA methylation pattern as well as in controlling DNA methylation states[2]. Alterations in DNA methylation in the promoter of MeCP2 were shown in autistic brains linking autism, DNA methylation and MeCP2[3]. Epigenetic variation is predicted to be a potentially more common cause of dysregulation to synaptic pathways[3]. A compelling reason to investigate epigenetic mechanisms in idiopathic autism is that such modifications can be influenced by exposure to biological modulators and environmental factors. Epigenetics may thus mediate the interaction between genotype and intrinsic (biological) or extrinsic (environmental) factors contributing to ASDs. Of all the epigenetic modulations, DNA methylation has the most established role in-regulation of promoter activity and gene regulatory regions[4]. At least two mechanisms have been demonstrated for inhibition of gene activity by DNA methylation. A methyl group positioned in a recognition element for a transcriptional factor can block binding of the transcription factor to the promoter[5,6].

Alternatively, methylated DNA attracts methylated DNA binding proteins such as the Rett syndrome protein methyl-CpG binding protein 2 (MeCP2), which in turn recruit histone modification enzymes such as histone deacetylases (HDAC)s to the gene precipitating an inactive gene silencing chromatin configuration[7].

Nutritional modification of DNA methylation

Nutritional modification of DNA methylation can have profound effects on phenotypic outcome of social animals. As normal activity of the methionine cycle metabolites is important for methylation, there has been a considerable effect of nutrients on DNA methylation. Folate, a water-soluble B vitamin, has been extensively studied for its effect on DNA methylation[8] because folate carries a methyl group and ultimately delivers that methyl group for the synthesis of AdoMet, the unique methyl donor for DNA methylation reactions. However, folate is not the sole

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determinant of DNA methylation, because other methyl donor nutrients such as methionine, choline, betaine, and vitamin B-12 as well as other environmental factors can also change DNA methylation status.

Vitamin B-12, a water-soluble B vitamin and essential cofactor of methionine synthase in 1-carbon metabolism, has been known to affect genomic DNA methylation. Most recently, Uekawa et al.[9] demonstrated that severe vitamin B-12 deficiency induces promoter hypomethylation of the cystathionine b-synthase gene and represses this gene transcription in rats, even though supplementation with methionine, the precursor of AdoMet and product of methionine synthase, could not reverse this effect. Choline is a methyl donor nutrient and maternal choline availability is essential for foetal neurogenesis such as hippocampal development as well as memory function throughout life. In a mouse study, choline deprivation during the embryonic period caused hypermethylation of a specific CpG site within the calbindin 1 (Calb1) gene, which is important in hippocampus development, along with increased expression of Calb1[10]. This study indicated that choline deficiency during the embryonic period could change DNA methylation and thereby alter foetal brain development.

Muratore et al.[11] suggested that Autistic children exhibit evidence of oxidative stress and impaired methylation, which may reflect effects of toxic exposure on sulphur metabolism. They reviewed the metabolic relationship between oxidative stress and methylation, with particular emphasis on adaptive responses that limit activity of cobalamin and folate-dependent methionine synthase.

Methionine synthase activity is required for dopamine-stimulated phospholipid methylation, a unique membrane-delimited signalling process mediated by the D4 dopamine receptor that promotes neuronal synchronization and attention, and synchrony is impaired in autism. Genetic polymorphisms adversely affecting sulphurmetabolism, methylation, detoxification, dopamine signalling and the formation of neuronal networks were found to occur more frequently in autistic subjects[11].

Steegers-Theunissen et al.[12] investigated whether periconceptional maternal folic acid supplementation affects methylation at the differentially methylated region (DMR) of the insulin-like growth factor 2 gene (IGF2) in 120 children aged 17 months. Eighty-six mothers of these children had used folic acid periconceptionally but 34 mothers had not. Children of mothers who used folic acid had a 4.5% higher methylation of the IGF2 DMR than children who were not exposed to maternal folic acid supplementation ($P = 0.014$). This result indicates that periconceptional folic acid supplementation is associated with imprinting status of IGF2 in the child, which may affect intrauterine programming of growth and development with consequences for health and disease throughout life. This study indicated that dietary methyl nutrients during the periconceptional period can change DNA methylation patterns in offspring and it may modify adult health-related phenotype. Animal studies also suggest that dietary folate during the postweaning period also affects DNA methylation status in a way that may modify disease susceptibility in later life.

There have been several studies of the nutritional and metabolic status of children with autism, but each focused on study of only a few biomarkers. Three studies have demonstrated that children with autism have impaired methylation, decreased glutathione, and oxidative stress[13,14,15], the sample sizes of these studies were very small to bring about meaningful interpretation but demonstrated that nutritional supplementation (with vitamin methyl-B12, folinic acid, and trimethylglycine) is beneficial. One study in Romania found normal levels of vitamin B12 and folate in children with autism compared to controls, but low levels of plasma glutathione[16]. One study of dietary intake of 111 autistic children in China found that most had inadequate intake of folic acid, vitamin B6, vitamin A, Vitamin C, and zinc[17].

Recommendations for Future Research

Future research should be targeted on the hypothesis that deficiencies in methyl donors (folate, and Vitamin B-12, choline) or oxidative stress or both may lead to impaired methylation, leading to neurological deficits, thereby causing Autism Spectrum Disorders. Further, Decreased DNA methylation increases expression of critical genes under the negative influence of methylation that participate in oxidative stress, inflammatory response and brain morphogenesis. Increased DNA methylation of the promoter region of certain critical genes (MeCp2) is a possible mechanism for increased gene silencing and decreased protein abundance in the autistic brain. The most exciting implication of epigenetics is that as "Gene expression" can be altered during development, it can also be altered later in life to reverse these modifications.

Weaver et al.[18], raise the intriguing possibility that epigenetic modifications during development and adulthood could be influenced by dietary modification of methylation, pharmacological agents or social interventions that might offer a therapeutic avenue for the treatment of a range of disorders of the nervous system. If the hypothesis is proved then the ability of a regimen of folinic acid, betaine and methylcobalmin to normalize plasma levels of sulphur metabolites (e.g cysteine) would indicate that methylation support and anti-oxidant strategies are likely to be useful in treating autism.

Conclusion

DNA methylayion marks are stable, yet potentially reversible. As these variations are reversible and dynamic, there is possibility of reversing maladaptive DNA methylation marks by dietary intake of certain metabolites like folinic acid, betaine, methylcobalmin cysteine and pharmacological agents which can therefore help in formulating preventive, diagnostic and therapeutic strategy. These advancements may be useful in the

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diagnosis and eventual treatment of autism and autism spectrum disorders.

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