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Epigenetic Influences upon Autism Spectrum Disorder

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Commentary

Epigenetic alterations underlying the neurodevelopmental aspects of Autism Spectrum Disorders (ASD) are emerging as important risk factors for disease pathogenesis. These influences present the case that gene expressions may sustain alterations at higher levels of complexity than modifications in the DNA sequence. Part-and-parcel and central to this notion, the phenomenon involves essential environmental impacting upon the gametes before conception. Genomic imprinting may be described as a process of silencing genes through DNA methylation with major effects upon placental biology, brain and functional development and the etiopathogenesis of neuropsychiatric disorders. It offers an epigenetic phenomenon through which some genes may be expressed in a manner that presents parent-of-origin-specificity and may be viewed as an essential mechanism for gene regulation based on chemical modifications of DNA and histone proteins. If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed. If the allele from the mother is imprinted, then only the allele from the father is expressed. Forms of genomic imprinting have been demonstrated in fungi, plants and mammals with over 150 imprinted in laboratory rodents [1,2]. Through forces of epigenetics, environmental factors, such as endocrine-disrupting agents and mental stress in early life, can alter epigenetic status and gene expression. In this regard, the epigenome, especially in the context of DNA methylation, provides a critical gene expression regulatory mechanism through which the normal and the pathologically anomalous brain development may proceed. Genomic imprinting and other epigenetic mechanisms involving environmental pressures have been found exert consequences and impinge on offspring neurodevelopment and the aberrant development of autism spectrum disorders [3]. ASDs offer an instance of the life-long existing disorders, such as attention-deficit hyperactivity disorder (AHDH), with a high level of heritability and complex conditions genetically, and despite several highly penetrant mutations in multiple genes being identified, these account for the etiology of less than one third of cases. The disorder is characterized by an impaired social communication profile and often repetitive, stereotyped behavior with evidence of regional brain dysconnectivity.

The abnormal methylation status of gene promoters of oxytonergic system has been implicated as among the etiologic factors of ASDs [4]. Here, it was shown that the methylation frequency of oxytocin receptor gene (OXTR) promoter from peripheral blood samples of children with autistic features. Their sample consisted 66 children, aged 22-94 months, with 27 children presenting ASDs, as diagnosed by DSM-IV-TR and the Childhood Autism Rating Scale and 39 children with autistic-like symptoms absent as the healthy control group. They examined the DNA methylation status of OXTR promoter by methylation specific enzymatic digestion of genomic DNA and polymerase chain reaction. Marked relationships were obtained between ASDs and healthy controls for the reduction of methylation frequency of the regions MT1 and MT3 of OXTR. Nevertheless, they did not obtain any association in the methylation frequency of MT2 and MT4 regions of OXTR. Despite their findings indicating a high frequency of OXTR promoter hypomethylation in autism disorder it is evident that a larger sample was necessary and for the independent replication of these results in a bigger sample set. The disorder etiopathogenesis of ASD appears to hinge not only on the 'genetics' of autism but also on the combinational roles of epigenetics, transcriptomics, immune system disruption and environmental factors [5]. Reelin, a large secreted extracellular-matrix glycoprotein facilitates the regulation of neuronal migration and cell positioning during early brain development through expediting cell-cell interactions and maintains its role through the life cycles of childhood, adolescent and adult brain progressions. Unsurprisingly, a surfeit of reelin gene expression, in both the CNS and peripheral nervous system, constitutes a risk factor for autism [6-8] with male heterozygous reeler (rl (+/-)) mice show an autism-like phenotype, including Purkinje cells (PCs) loss, behavioral rigidity and a broad spectrum of sensory dysfunction/dysregulation [9]. During puberty, methylation of the reelin gene appears to be initiated since hypermethylation is observed in post-mortem brains of neuropsychiatric patients [10-12] observed autistic-like characteristics and mitochondrial abnormalities in male rl (+/-) mice following exposure to high doses of methyl mercury. Lintas et al. have shown that post-mortem analyses of autistic patients expressed markedly higher numbers of methylated CpG islands and greater methylation in the 5' region of the RELN gene promoter, spanning from -458 to -223 bp, whereas the compared control brains expressed more methylated CpG positions and greater extent of methylation at the 3' promoter region, spanning from -222 to +1 bp, with the upstream promoter region (-458 to -364 bp) showing methylation only in patients brains, whereas the most downstream region (-131 to +1 bp) was methylated exclusively in the control brains [13]. The authors concluded that the pattern of methylation differed between ASD patients' and the control brains, with ASD-specific CpG positions conferring risk through 'blunting' reelin gene expression.

In a search for methylation changes on blood DNA of 53 male ASD patients and 757 healthy controls, Homs et al. obtained 700 differentially methylated cytosine-guanine sites (CpGs) most of which were hypomethylated among the autistic patients (83.9%), with cis-acting expression changes at 7.6% of locations, including (a) Hypomethylation induced by rare genetic variants (meSNVs), in spite of the notion that the disorder arises from common gene variants, at six loci (ERMN, USP24, METTL21C, PDE10A, STX16 and DBT) significantly associated with ASD (q-value <0.05); and (2) Clustered epimutations linked to transcriptional changes in single-Autism patients (n=4) [14,15]. All themeSNVs and clustered 'epi-mutations' were inherited from unaffected parents. The resequencing of the top candidate genes also revealed a markedly incremented load of deleterious mutations affecting ERMN in ASD compared with the control group. Kubota et al. have demonstrated that environmentally-

induced epigenetic changes are not abolished during gametogenesis and are transmitted to subsequent generations, leading to changes in behavior phenotypes [16]. Nevertheless, epigenetics presents a reversible nature since these effects are based on the addition or removal of chemical residues thereby allowing the original epigenetic status may be resumed. For this reason, a variety of therapeutic drugs used for psychiatric disorders including, including autism, may re-establish the initial epigenetic state and gene expression. Keil et al. have outlined epidemiological and experimental results that implicate expressions of altered DNA methylation that constitute a potential mechanism through which environmental chemical agents bestow the risk for ASD diagnosis, e.g. as illustrated by polychlorinated biphenyls (PCBs), lead and bisphenol A (BPA) applications [17].

In conclusion, the emerging evidence implies patterns of epigenetic changes in the brains of ASD patients expressed during the earliest phases of nervous system development. These alterations confer a general dysregulation of gene expression that exacerbate disturbances to the chronological schemata of neural maturation and patterning thereby instigating disorder susceptibility.

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