News

Research Highlights

New insights into the biological mechanism of autism

In a recent study published in *Molecular Psychiatry*, a group of researchers from King's College London (London, UK) studied identical twins in order to identify epigenetic changes involved in autism spectrum disorder (ASD).

ASD describes a group of complex neurodevelopmental disorders that differ in severity among sufferers. It is characterized by a varying degree of impairment in three areas: deficits in social interactions and understanding; repetitive behavior and interests; and language and communication deficits.

Previous evidence from twin studies has shown that ASD has a strong genetic component. However, there is significant discordance within monozygotic twin pairs and often notable differences in symptom severity, indicating a role for epigenetic factors. Given that they have identical gene sequences, monozygotic twins provide an excellent model for examination of these epigenetic factors.

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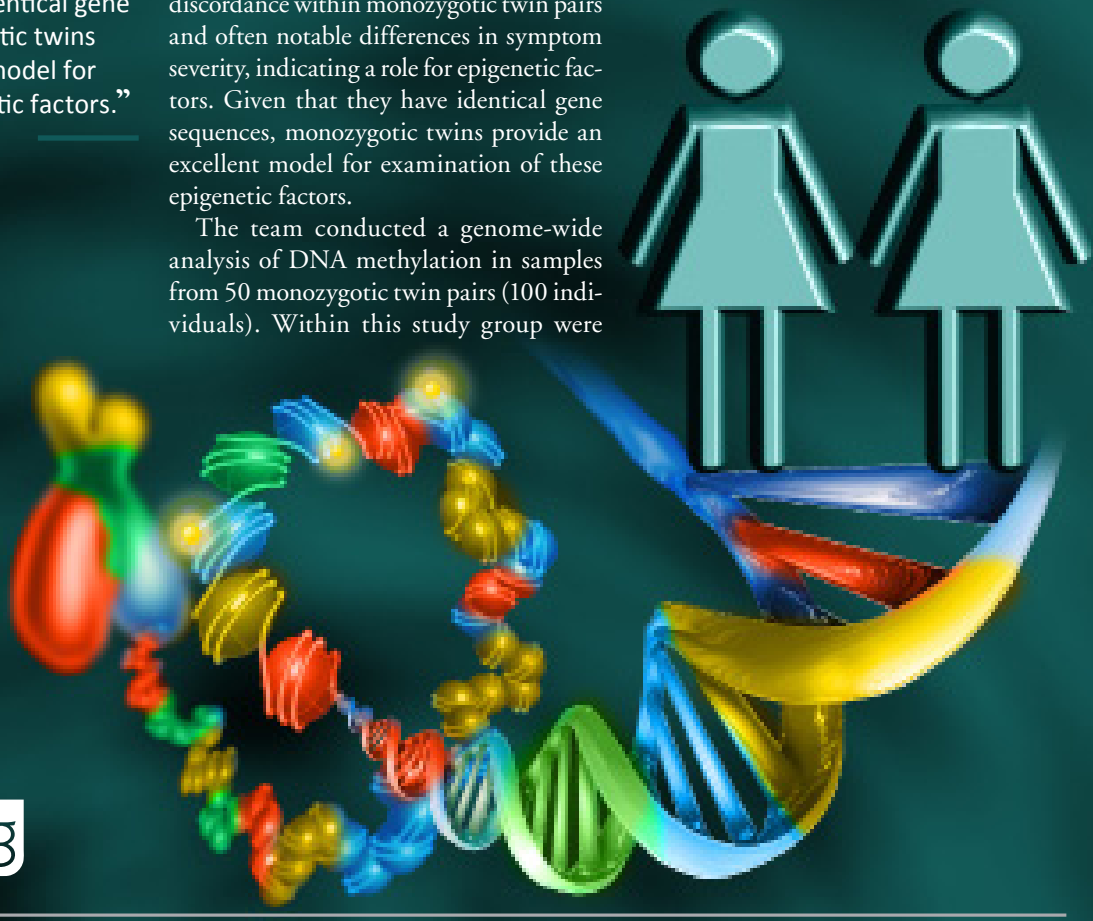
The team conducted a genome-wide analysis of DNA methylation in samples from 50 monozygotic twin pairs (100 individuals). Within this study group were twins discordant and concordant for ASD and autism-related behavior traits, as well as those with no autism phenotype. Within-twin and between-group analyses were carried out in order to identify any patterns of change in DNA methylation.

It was noted that DNA methylation was consistently altered at some sites for all ASD sufferers, while other sites of methylation appeared to be specific for certain diagnostic categories. The team observed a significant correlation between DNA methylation at multiple CpG sites and quantitatively rated autistic trait scores, with considerable epigenetic heterogeneity between the three autistic trait domains. Epigenetic modifications were observed



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at several genes previously implicated in autism and some disease-associated DNA methylation alterations were also observed at loci that had not been previously implicated.

This is the first large-scale study to analyze the genome-wide variation in DNA methylation in monozygotic twins discordant for ASD and autism-related traits. This study implicates altered DNA methylation in the pathology of autism; however, genome-wide analyses across larger cohorts are required to establish the extent of the impact of ASD-associated epigenetic variations. By identifying key epigenetic changes common to ASD sufferers, it may become possible to develop therapeutic interventions.

Source: Wong C, Meaburn E, Ronald A et al. *Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioral traits.* Mol. Psychiatry *doi: 10.1038/mp.2013.41 (2013) (Epub ahead of print).*

Epigenetic mechanisms behind lung development and repair

In a recent study that was published in *Developmental Cell*, researchers from the Penn Institute for Regenerative Medicine in the Perelman School of Medicine, University of Pennsylvania (PA, USA) investigated the mechanisms by which epigenetics may control lung development and repair.

Chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are common and affect the small airways of the lung, causing a reduction in the normal repair mechanisms. It has previously been demonstrated that COPD patients display a reduction in the levels of HDAC2 expression and activity. This has led to the hypothesis that decreased histone deacetylase (HDAC) activity may impede the regenerative capacity of the lung epithelium.

The team demonstrated that HDAC1 and HDAC2 specifically regulate the development of $Sox2^+$ progenitor cells in the lung. It was observed that HDAC1/2 deficiency was associated with a loss of expression of the key transcription factor Sox2 and, hence, a loss of proximal airway development. By contrast, postnatal HDAC1/2 deficiency was associated with an increased expression of the cell-cycle regulators Rb1, p21/Cdkn1a and p16/Ink4a, leading to loss of cell-cycle progression and inhibited regeneration of $Sox2^+$ lung epithelium.

These results highlight a role for HDAC1/2-mediated mechanisms in the regulation of the development and regeneration of lung tissue. This opens up the possibility of treating diseases, such as asthma and COPD, with therapies that target HDACs. A selection of HDAC inhibitors and activators are currently in clinical trials for the treatment of other diseases, so it is possible that in the future they may be used for this indication.

Source: Wang Y, Tian Y, Morley M et al. *Development and regeneration of Sox2 endoderm progenitors are regulated by a HDAC1/2–Bmp4/Rb1 regulatory pathway.* Dev. Cell *24(4), 345–158 (2013).*

Epigenetic changes found to be associated with childhood brain cancer

Researchers at Rockefeller University (NY, USA) have discovered a potential mechanism by which a mutated histone protein may lead to the development of a rare childhood brain cancer, namely diffuse intrinsic pontine glioma (DIPG).

> "The team analyzed human diffuse intrinsic pontine glioma tumors, observing significantly lower levels of histone H3 methylation in gliomas containing the K27M mutation."

This study, published in *Science* Express, is one of a series of recent studies that demonstrate a direct link between a mutated histone protein and DIPG. The reported mutations occur on histone H3. The sequencing of samples from pediatric gliomas has identified missense mutations in which lysine is substituted for methionine (K27M) in genes encoding histone H3, thereby silencing the associated gene.

The team analyzed human DIPG tumors, observing significantly lower levels of histone H3 methylation in gliomas containing the K27M mutation. Significantly, histone H3K27M transgenes are sufficient to cause a reduction in the methylation levels of normal H3 histones.

It was determined that the mutated histone H3 interacts with the EZH2 subunit of the histone methyltransferase PRC2, thereby inhibiting its enzymatic activity and causing a reduction in the methylation of normal H3 histones. This reduction in methylation is likely to cause the activation of pathways that promote the growth of tumors in DIPG.

This study is the first to link a histone mutation to a disease. By creating a model for the mechanism by which aberrant epigenetic silencing through the inhibition of PRC2 by a mutant histone may lead to disease, it may be

possible to therapeutically target these mechanisms. It is also proposed that lysine-to-methionine mutations may lead to aberrant alterations of epigenetic states in other pathologies.

Source: Lewis P, Muller M, Koletsky S et al. *Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma.* Science *doi:10.1126/science.1232245 (2013) (Epub ahead of print).*

Placental tissue analysis aids the understanding of DNA methylation

A recent study conducted by researchers from the University of California, Davis (CA, USA) and the University of British Columbia (Vancouver, Canada) and published in the *Proceedings of the National Academy of Sciences of the United States of America* has helped to expand our knowledge of DNA methylation.

In the majority of human tissues, a significant proportion of the genome is highly methylated (>70%). Recent studies have demonstrated the presence of large partially methylated domains (PMDs) in some human cell lines. These were found to cover up to 40% of the genome and were associated with gene repression. Until now, PMDs have only been identified in cell lines.

In this study, the team analyzed placental tissue; a tissue that has numerous invasive characteristics that are often associated with cancer. The team performed sequencing analysis of bisulfate-treated DNA in samples of full-term human placenta. PMDs were shown to cover 37% of the placental genome, including approximately 17% of all genes. In low-methylation areas, these genes were less likely to be transcribed. The study also highlighted the presence of more highly methylated CpG islands in PMDs, which are generally associated with gene transcriptional silencing of promoters.

This study represents the first time that PMDs have been found in regular human tissue. The study's results enhance our understanding of epigenetics, and suggest that PMDs are relevant for both normal development and cancer, which may be useful for the future discovery of biomarkers.

Source: Schroeder D, Blair J, Lott P et al. *The human placenta methylome.* Proc. Natl Acad. Sci. USA *110(15), 6037–6042 (2013).*

Epigenetic mechanisms connect inflammation-associated diseases

A recent study conducted by researchers at Boston University School of Medicine (MA, USA) and published in the *Journal of Immunology*, has highlighted the epigenetic mechanisms connecting a variety of inflammation-associated diseases.

Histone acetylation is a mechanism known to regulate the activation of multiple inflammatory genes. It is understood that histone acetylation plays a critical role in chronic inflammatory diseases but, until now, the proteins responsible for the translation of this acetylation into an inflammatory response have not been well characterized.

It has been previously demonstrated that the gene, *Brd2*, is associated with high insulin production and expansion of adipose stores, driving obesity when levels are low and cancer when Brd2 levels are high. Brd2 is a member of the BET family of dual bromodomain-containing transcriptional regulators, which are hypothesized to directly control inflammatory genes.

The team used *brd2 lo* mice (a BET protein hypomorph) as a model to demonstrate that Brd2 is necessary for the production of proinflammatory cytokines in macrophages. The same result was observed with RNA knockdown and a small-molecule inhibitor of BET protein binding. It was also demonstrated that Brd2 and Brd4 physically associate with the promoters of genes responsible for the proinflammatory response in macrophages.

These results demonstrate that, through the induction of proinflammatory cytokine production, proteins in the BET family may direct the pathogenesis of many hyperinflammatory diseases. It is, therefore, proposed that small-molecule inhibitors against BET proteins may be a therapeutic avenue to help decrease the inflammatory response associated with diseases such as obesity, Type 2 diabetes, cancer and sepsis.

Source: Belkina A, Nikolajczyk B, Denis G et al. *BET protein function is required for inflammation:* Brd2 *genetic disruption and BET inhibitor JQ1 impair mouse macrophage inflammatory responses.* J. Immunol. *190(7), 3670–3678 (2013).*

– All stories written by Caroline Telfer

About the News and Views

The News and Views highlights some of the most important events and research in epigenomics. If you have newsworthy information, please contact:

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