VIEWPOINT

Chemical tags reveal interplay of genes, environment in autism

BY **JANINE LASALLE**

20 JUNE 2017

The letters A, T, G and C, which represent different DNA bases, spell out the blueprint for the human body. But they aren't the only ones that matter.

CH3 is the chemical formula for a methyl group — a carbon atom studded with three hydrogens. Methyl groups can attach to DNA and affect whether the DNA is recognized by the cell's machinery. Different exposures and experiences — anything from air pollution exposure to stress — can make DNA more or less likely to gain or lose methyl tags.

This process of DNA 'methylation' is where genetic and environmental influences collide — where nature meets nurture.

DNA methylation is just one example of a chemical tag on DNA. Collectively, these chemical, or '**epigenetic**,' tags do not change the genetic code but can alter genes in ways that affect the brain and behavior.

Many of the genes mutated in people with autism are involved in epigenetic processes of adding or removing tags in the developing brain. Some children with autism have atypical patterns of DNA methylation in their **blood** and **saliva**. And a small number of studies using postmortem brain tissue from people with autism have revealed **atypical methylation** patterns on genes that help neurons connect with each other.

Studying epigenetic changes in people with autism could reveal clues to autism's genetic and environmental roots. Because chemical tags on DNA are easier to change than the DNA sequence itself, these studies could also point to new treatments.

Tag team:

The location of the methyl groups — the sites at which they attach to DNA — matters. In mammals, the tags stick to the DNA letter C, which stands for cytosine. And they usually attach to C's that are followed by a G, for guanine. This type of methylation is called mCG. Roughly 80 percent of CG sites in the brain are methylated[1].

Most mCG methylation occurs during early embryonic development, around the time that a fertilized egg implants into the womb.

When a methyl group attaches to a C followed by any letter other than G, it is called mCH methylation. Most mCH methylation occurs as neurons form connections with each other, called **synapses**, during childhood and early adolescence[2]. Earlier this year, researchers reported that levels of mCH methylation are **enhanced in brain tissue from people with autism**[3].

Methyl groups also attach to histones, proteins inside the nucleus that help to keep DNA compact and organized. Histone methylation is also **altered in postmortem brain tissue** from people with autism[4]. Methyl groups on histones activate regions of the genome that regulate gene expression, called promoters and enhancers. It's these methyl groups that help to make sure genes make proteins at the right time and place in the body.

Supply and demand:

Clearly, methyl groups play a crucial role in determining which genes are expressed in a given cell at a given time. But they have other functions, too.

For instance, they are an essential molecular ingredient in the signaling molecules, or **neurotransmitters**, that neurons use to communicate. That means there is a high demand for methyl groups, and a limited supply.

The major source of new methyl groups is food — including green leafy vegetables, beets, fish and eggs. Some women may need a greater supply of dietary methyl donors or nutritional supplements than others during pregnancy, depending on how they are genetically programmed to metabolize food. Because most brain methylation occurs shortly after conception, this is a crucial time for women to have a diet rich in methyl donors.

Cells are great at recycling old molecules, including methyl groups, for new parts. But this recycling process requires energy that is sometimes tied up in other cellular processes, such as the removal of toxins[5]. Exposure to air pollution and certain chemicals in our food, water and homes can interfere with the recycling of methyl groups. These exposures may represent environmental risk factors for autism that operate through epigenetic mechanisms.

Although the body has systems — and backup systems — to keep the supply of methyl groups in good standing, genetic and environmental factors can interact to challenge these systems all at

once, as they may in autism[6].

Investigating interactions:

We found evidence for an interaction between genetic, environmental and epigenetic risk factors for autism last year. Postmortem brain tissue from people with a duplication of DNA on chromosome 15 contains unusually high levels of a pollutant known as PCB 95[7]. This chromosomal duplication is associated with autism. PCB 95 comes mostly from dietary sources such as fish, dairy and meat. And it accumulates in fatty tissues, including the brain.

We tested the effects of the duplication by itself and in combination with PCB 95 exposure in a human neuronal cell line. We found that certain genes have fewer methyl groups than expected in neurons with the duplication. Some of these genes are similarly under-methylated in neurons exposed to PCB 95 alone.

When we exposed neurons with the duplication to PCB 95, we saw a dearth of methyl groups for even more genes. Some of the neurons spontaneously acquired a second duplication in chromosomal region 22q. These neurons had the lowest proportion of methylated genes.

We must continue to investigate the combinatorial effects of genes and environmental factors as they relate to autism. To study this in living people, some researchers are using markers of methylation in surrogate tissues, such as placenta and cord blood, to represent risk factors at birth. Knowing which markers correlate with autism risk could open the door to treatments that target epigenetic processes at a critical time of development.

Janine LaSalle is associate director of genomics at the University of California, Davis, Genome Center.

REFERENCES:

1. Ciernia A.V. and J. LaSalle. *Nat. Rev. Neurosci.* **17**, 411-423 (2016) **PubMed**
2. Lister R. *et al*. *Science* **341**, 1237905 (2013) **PubMed**
3. Ellis S.E. *et al. Mol. Autism* **8**, 6 (2017) **PubMed**
4. Shulha H.P. *et al. Arch. Gen. Psychiatry* **69**, 314-324 (2012) **PubMed**
5. Lee D.H. *et al*. *Environ. Health Perspect.* **117**, 1799-1802 **(**2009) **PubMed**
6. O'Roak B.J. *et al*. *Nat. Genet.* **43**, 585-589 (2011) **PubMed**
7. Dunaway K.W. *et al*. *Cell Rep.* **17**, 3035-3048 **(**2016) **PubMed**