# NEUROLOGIC DISORDERS NEWS ARTICLE

## Unexpected role of reduced myelination in Williams syndrome

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Researchers have discovered that myelination and conduction are reduced in the neurodevelopmental disorder Williams syndrome, and identified two FDA-approved drugs commonly used for the treatment of multiple sclerosis (MS) that may have the potential to provide future clinical therapeutic benefit for patients with Williams syndrome.

The scientists published their findings in the April 22, 2019, issue of *Nature Neuroscience*.

Lead investigator Boaz Barak, of Tel Aviv University, working in collaboration with Guoping Feng at the Massachusetts Institute of Technology, used *Gft2i* frontal lobe knockout mice to model Williams syndrome, including similar hypersocial behavior, and they were able to ameliorate some of the deficits in a mouse model of Williams syndrome using clemastine fumarate and 4-aminopyridine.

After discovering the reductions in myelination in mice, they examined human tissue bank samples from deceased Williams syndrome patients and discovered similar reductions in myelination.

Currently, the only treatments for Williams syndrome are medications that address attention deficit hyperactivity disorder (ADHD), anxiety and other symptoms, but these do not address the basic pathophysiological mechanism.

Now researchers can test whether these two FDA-approved drugs may be relevant in Williams syndrome.

The genetic mechanism of Williams syndrome involves a micro-deletion of 25 genes on chromosome 7. Instead of manipulating all of the genes that may be relevant to this disorder, investigators sought to find the neurobiological mechanism that can explain the typically hypersociability of those patients.

Previously, heterozygous loss of the singular gene *Gtf2i* (general transcription factor IIi) within this cluster was already known to confer increased sociability similar to Williams syndrome. So researchers manipulated only *Gtf2i* out of those 25 genes.

**Neuronal deletion affects oligodendrocytes**

Because homozygous deletion of *Gtf2i* in the whole animal is lethal, the team induced the homozygous deletion of *Gtf2i* only in excitatory neurons of the forebrain. The forebrain is a brain region that has several structures, including the outer cortex, hippocampus and amygdala, which are all key brain regions related to social behavior.

By manipulating *Gtf2i* only in the excitatory neurons researchers observed Williams syndrome characteristic hyper-social phenotype with increased nonsocial-related anxiety, abnormal fine motor skills deficit and neuroanatomical abnormalities.

Researchers also examined heterozygous *Gtf2i* loss of function in the whole mouse just like in the human disease. They observed increased social behavior and nonsocial anxiety. They also made the unexpected discovery that there were deficits in myelin abundance.

They found a novel pathophysiological link to mmyelination deficits to Williams syndrome. This myelination deficit was then revealed upon examination of human tissue samples from Williams syndrome patients.

The *GTF2I* gene was significantly down-regulated in the tissue samples of Williams syndrome subjects as well. The histology level in the Williams syndrome patient-derived brain tissue revealed thinner myelin with decreased number of the oligodendrocytes, validating their findings from mouse models.

Barak told *BioWorld Science* that he has met several Williams syndrome patients in both the U.S. and Israel. He learned not only of the hyper-sociability that was known but also their fine motor skill deficits. When he discussed this with them and their caregivers, they described some of the features that he first encountered in the mouse models. Barak said this was very emotional for him, because it is important for him to emphasize that his studies were not only in mice.

Barak explained that his laboratory focuses on understanding the neurobiological mechanisms of abnormal social and anxiety behavior. In particular, his laboratory focuses on Williams syndrome and autism, since these two syndromes have opposite social behavior phenotype. These new findings have linked myelination abnormalities to social behavior abnormalities to focus on the interplay between myelin and social behavior.

The other aspect of particular interest is to determine how a defect in the neuron can affect the myelination. Principal investigator Guoping Feng does not believe this reduction in myelination is very specific to Williams syndrome. Feng explained to *BioWorld Science*, "There are a lot of studies that suggest that if you have a defect in neuronal activity, then it will affect the myelination and development. So we think that maybe this is a more common phenomenon in a subset of neurodevelopmental disorders, such as in autism spectrum disorders, and in some

forms of the monogenic forms of severe autism. For example chd8, which is one of the monogenic causes of autism spectrum disorder, also affected [myelination] in mouse models. So one aspect we want to look at is whether myelination is a more general defect in a subset of neurodevelopmental disorders outside of Williams syndrome and perhaps there's some kind of a convergent mechanism."

"This will be a very exciting area to figure out what are the signals back and forth between the neuron and oligodendrocyte and how they are promoting or regulating in the formation of myelin," he added.

Barak concurred. "If we can define this molecule specifically, this will contribute not only to Williams syndrome, then this will contribute to the myelination of related disorders such as multiple sclerosis, autism, now we know Williams syndrome, Alzheimer's disease, and many other neurological disorders and also related disorders that involve myelin," he said. "If we will be able to define what molecule is missing, we will be able to better understand what could be a drug target to rescue myelin abnormalities."

(Barak, B. et al. Nat Neurosci 2019, 22: 700).