Team finds differences in RORA levels in brain may contribute to autism sex bias

27 May 2015

George Washington University (GW) researcher Valerie Hu, Ph.D., has found an important sex-dependent difference in the level of RORA protein in brain tissues of males and females. Specifically, females without autism have a slightly higher level of RORA in the frontal cortex of the brain than males without autism, while the levels of the protein are comparably lower in the brain of both males and females with autism. The new study, published this month by *Molecular Autism* in a special issue on sex differences in autism, further shows a stronger correlation between the expression level of RORA and that of genes regulated by RORA in males. This finding suggests males may be more susceptible than females to dysregulation of multiple genes under conditions of RORA deficiency.

"According to the Centers for Disease Control and Prevention, males are nearly four times more likely than females to have autism, but the reason for this sex bias is still a mystery," said Hu, professor of biochemistry and molecular medicine at the GW School of Medicine and Health Sciences. "Our research suggests that deficiencies in RORA expression in the brain may have a greater impact on males, which may contribute to the known sex bias in autism in several ways."

In previous studies, Hu and her group reported that RORA is a novel candidate gene for autism and is regulated in opposite directions by male and female hormones. They later showed that RORA, a nuclear hormone receptor that functions as a transcription factor, can potentially regulate the transcription of more than 2,500 genes, including over 400 genes already associated with autism. This finding suggests a domino effect in which RORA deficiency can impact many autism genes. Among the genes they validated as transcriptional targets of RORA is the gene for aromatase, an enzyme that converts male to female hormones. Thus, RORA deficiency is linked to aromatase deficiency, which in turn can lead to elevated testosterone levels, a proposed risk factor for autism.

Using a genetically identical mouse model to reduce the contribution of genetic heterogeneity to gene expression that is typical for humans, the group observed a two-fold higher level of RORA expression in the frontal cortex of female mice in comparison to male mice. Moreover, the correlation between RORA and target gene expression in the cortex is much higher in male mice. They also found a strong positive correlation between the levels of RORA and aromatase proteins in the frontal cortex of human males and females without autism spectrum disorder and of males with autism spectrum disorder. However, this strong correlation between RORA and aromatase levels was not observed in females with autism spectrum disorder, suggesting that they may have compensatory mechanisms for regulating RORA target genes to offset RORA deficiency.

"Overall, this study suggests that RORA deficiency may have a greater impact on males, not only because males have lower baseline levels of RORA in the brain to start with, but also because the expression of autism-associated genes may be more highly correlated with the lower expression of RORA in males," said Hu. "This provides yet another plausible explanation for sex differences in autism susceptibility."

More information: "Investigation of sex differences in the expression of RORA and its transcriptional targets in the brain as a potential contributor to the sex bias in autism" is published in the open access journal *Molecular Autism*. The research article is freely available at www.molecularautism.com/content/6/1/7.

Provided by George Washington University