HOT TOPICS

Genetic and epigenetic modulation of the oxytocin receptor and implications for autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication impairments and repetitive behaviors that result from genetic and epigenetic factors. Three decades of research have demonstrated that the oxytocin system is a key modulator of social behavior and is therefore one of the most promising systems to target in ASD. Emerging evidence indicates that intranasal oxytocin (IN-OT) enhances social functioning in some individuals with ASD and modulates activity in the social brain network [1]. Translating research innovation into successful treatment requires the discovery of biomarkers of treatment efficacy in ASD. As analytically accessible factors that can influence oxytocin receptor (*OXTR*) expression, genetic, and epigenetic variation in *OXTR* could be key predictors of exogenous oxytocin treatment efficacy.

DNA methylation is a major epigenetic mechanism that regulates gene transcription and can be inherited or influenced by early life experience [2]. Increased *OXTR* DNA methylation in the periphery is associated with decreased *OXTR* gene expression in the brain [2]. *OXTR* DNA methylation has been associated with sociality in neurotypical individuals [3]. We recently showed that ASD males exhibit *OXTR* DNA hypermethylation relative to neurotypicals [4], a finding that is in line with a previous report [5]. Importantly, *OXTR* DNA hypermethylation was associated with reduced resting state functional connectivity between brain areas involved in theory of mind (superior temporal sulcus and posterior cingulate gyrus). Moreover, higher *OXTR* DNA methylation at another CpG site was associated with lower social responsiveness in ASD and with hyperconnectivity between reward areas (ventral striatum and ventromedial prefrontal cortex). Interestingly, those with high DNA methylation at this CpG site reported more restricted interests in programming, coding, trains, game development, electronics, Star Wars, and astronomy. Associating specific subtypes of autism with specific epigenetic biomarkers might facilitate early ASD diagnosis. More research is needed to evaluate the specificity of *OXTR* DNA hypermethylation at specific sites to autism diagnosis.

Methylation of *OXTR* may be able to identify ASD subtypes (such as those with less methylation) that will respond optimally to IN-OT treatment in future trials. Supporting evidence for this hypothesis comes from our recent finding that neurotypical men and women with lower *OXTR* DNA methylation display increased brain activity in visual attention areas following IN-OT intake [6].

Recent studies report that IN-OT effects on responses to social stimuli are modulated by SNPs within the gene that codes for *OXTR*. Specifically, *OXTR* SNPs have been reported to modulate

IN-OT effects on the caudate nucleus response to positive social interactions in neurotypicals [7] and on the brain activity and social functioning in autism [1]. Several studies examining SNP rs53576 consistently found the G allele or GG genotype to be more responsive to IN-OT. The underlying assumption in this work has been that *OXTR* SNPs modulate IN-OT effects by influencing *OXTR* expression. The Genotype-Tissue Expression (GTEx) Portal identifies many human *OXTR* SNPs, including rs53576, as being significantly associated with *OXTR* expression in various brain areas. These new data allow investigators to systematically target SNPs known to affect *OXTR* expression when testing for *OXTR* modulation of IN-OT effects in social behavioral disorders.

Identifying genetic and epigenetic biomarkers that predict treatment efficacy is in line with a personalized medicine approach that will lead to breakthroughs in psychiatry.

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AUTHOR CONTRIBUTIONS

EA conceived the topic of the paper and wrote the paper. JR contributed to the conception and the writing of the paper.

ADDITIONAL INFORMATION

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