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Sex-specific neurotoxicity as possible cause of regressive autism

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Autism is an increasing neurodevelopmental disorder that appears by 3 years of age, has a striking male prevalence and often shows comorbid situations, such as gastrointestinal (GI) disorders. Although some causative genetic variants have already been found, they affect only ~30% of cases and cannot explain the dramatic increase of autism in the last decades. As in other pathologies in which specific gene–environment interplay triggers the disease, the possible role of environmental factors, such as infections, xenobiotics and drugs in provoking autism in subjects with genetic susceptibility has been proposed. Among autism causative genes, we focused on neuroligine3 (NLGN3) and 4X (NLGN4X) because they play a key role in synaptic plasticity and, being located on X chromosome, are hemizygous in males. We analyzed some intronic and 3'UTR SNPS of NLGN3 and NLGN4X in 190 Italian autistic cases (male:female=4,4:1) by Sanger sequencing and High resolution Melting. Overall we found 3 SNPs haplotypes statistically significant in autistics comparing to the minor allele frequencies (MAF) from the 1000-Genomes Project CEU. Questioning bioinformatics predictive database it showed that some SNPs in the 3'UTR of NLGN4X may modify microRNA target sites. Interestingly, mining the literature we found, among xenobiotics, that ochratoxinA (OTA) and fumonisin B1, two of major food contaminating mycotoxins, provoke, in animal models, a neurological and immunological damage, especially in males. Moreover recent studies have also demonstrated that in *in vitro* and in *in vivo* experiments, these toxins modulated the level of some microRNAs. Surprisingly, OTA up-regulates some microRNA implicated in autism and in NLGN4X expression. In conclusion we speculate that a specific NLGN4X–mycotoxin interplay via 3'UTR SNPS- dysregulated microRNAs cross-talk could trigger autism in those patients suffering from gastrointestinal disorders and leaky gut. Further analyses are required to demonstrate this hypothesis and to define the effects of toxins on general population in order to establish the risk assessment and the daily tolerable intake.

Biography

Alessandra Mezzelani has completed her PhD in "Veterinaty Biotechnologies" in 1995 from Milan University. She has been worked as Associated Researcher at the "National Tumor Institute of Milan" for 6 years. She is staff researcher at the Institute of Biomedical Technologies, National Research Council of Italy, responsible for the "Translational Bioinformatics Lab" since 2001. She has published 51 papers in reputed journals.

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