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MATERNAL SKEWED X CHROMOSOME INACTIVATION AND NEURODEVELOPMENTAL DISORDERS RISK

Background. Neurodevelopmental disorders (NDDs) encompass a heterogeneous group of complex pathological conditions that affect brain structure and development [1]. Large-scale genomic studies confirm that NDDs are highly heritable, approaching estimates up to 90%. Despite WES/WGS promising results, ~30% of NDD cases can be explained by known genetic risk [2]. The possible association of genetic and epigenetic alterations that may influence maternal-fetal interactions, leading to NDD is a promising area of research. **The aim** of our study was to analyze the skewed X chromosome inactivation (XCI) in the mothers of NDD patients. **Methods.** The XCI was analyzed by methyl-sensitive PCR of AR gene CAG-poly-morphism (Xq12), which should randomly X-inactivate by hypermethylation. XCI was assessed by semiquantitative comparing the intensity of AR gene alleles, which were amplified from both native DNA and Hin6.I hydrolyzed DNA. The fractioning and allele analysis were performed in ALF-express II fluorescence analyzer and Fragment Manager software. **Results.** The study was conducted in compliance with bioethical standards after obtaining informed consent from the participants. The study group: 90 unrelated NDD patients and their mothers (age M = 35.7; SD = 7.0; Me = 35.0), the control group: 59 women from the population of Ukraine (M age = 36.8; SD = 8.5; Me = 34.4). XCI over 75% was detected in 30.7% of NDD mothers group, and in 5.7% of controls ($\chi^2 = 12$; $p = 0.0005$). Mothers of NDD patients have a 7-fold higher chance of having XCI than women without such familial cases (OR = 7.3; CI: 2.21–32.15). Extreme XCI of more than 90%, which is associated with pregnancy pathologies and the risk of cancer, was detected in the mothers' group only (9.4%) ($\chi^2 = 5.23$; $p = 0.02$). The association of extreme XCI with impaired fetal neural development is a prospect for further research. 16 out of 23 NDD patients (69.5%) inherited an X chromosome that is predominantly methylated in their mothers. The deviation from the expected inheritance distribution (1:1) is statistically significant ($p = 0.04$). **Conclusions.** XCI greater than 75% is associated with a risk of having a child with NDD. Besides, an inheritance of the maternally preferentially inactivated X chromosome is associated with the NDD occurrence in offspring.

Keywords: neurodevelopmental disorder, skewed X chromosome inactivation, mother-fetus genetic interaction.

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