Autism-related gene intergenerationally regulates neurodevelopment and behavior in fish through evolutionarily conserved mechanisms

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Résumé

Parental response to environmental stress can impact offspring through non-genetic changes in the gamete. While paternal stress affects epigenetic marks and non-coding RNAs in the spermatozoa, studies investigating maternal stress prior to fertilization are scarce and intergenerational mechanisms modulating offspring fitness and behavior are currently poorly understood. We investigated the intergenerational regulatory role of *auts2a* (*i.e.*, the medaka ortholog of *AUTS2*), a gene involved in neurodevelopmental disorders (NDD) in humans and down-regulated in the rainbow trout oocyte following maternal thermal stress. We developed a medaka model to assess the impact of paternal and maternal *auts2a* contribution in the offspring, independently of the genotype. We show that maternal, but not paternal contribution of *auts2a*, drives progeny neurodevelopment and shapes long-term behavior. The lack of maternal *auts2a* contribution leads to decreased cognitive abilities (*i.e.,* anxiety-like behavior and learning capacities), impaired macroscopic features and gene expression during neurodevelopment in the offspring. Genes dysregulated belong to conserved neurodevelopmental pathways, conserved transcription factors and are associated with NDDs. The lack of maternal *auts2a* contribution also modulates the expression of a limited number of conserved maternally-inherited post-transcriptional and post-translational regulators in oocytes, that are essential for early embryonic development prior to zygotic genome activation in vertebrates. Moreover, *AUTS2* is part of a maternally-inherited evolutionarily-conserved gene set associated with neurodevelopment, behavior and NDDs. Altogether, our results reveal that maternal *auts2a* alone is a major driver of neurodevelopment and long-term behavior and shed new light on mechanisms underlying non-genetic maternal transmission in vertebrates.

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