MAU2 is required for zebrafish neurodevelopment

S. Palermo[1], M. Tricco[1], M. Betti1, M. Spreafico[1], C. Gervasini[2], V. Massa[2], A. Fantin[1]

[1] University of Milan, Department of Biosciences, Milan, Italy;
[2] University of Milan, Department of Health Sciences, Milan, Italy.

Cohesin is a multisubunit protein complex involved in chromatin dynamics, with significant roles in sister chromatid cohesion, transcriptional regulation, and chromatin organization. The key for cohesin's functionality is the NIPBL-MAU2 heterodimer, known as the cohesin loader complex. Pathogenetic variants in NIPBL lead to Cornelia de Lange syndrome (CdLS), a cohesinopathy characterized by a spectrum of clinical features, including developmental delays, craniofacial abnormalities, intellectual disability, and limb anomalies. Recent findings suggest that MAU2 variants could also cause CdLS, indicating a shared pathogenic mechanism involving impaired cohesion-loader function. However, very little is known about MAU2 function and its impact on embryonic morphogenesis.
In this study, we aim to elucidate the role of MAU2 in neural and craniofacial development and CdLS insurgence by exploiting the zebrafish model. Gene expression analysis showed robust mau2 transcripts detection during zebrafish embryo development, which appeared enriched in the central nervous system, especially in the cephalic region. We then exploited a knockdown (KD) strategy by combining two different antisense morpholinos (MOs) to hamper Mau2 protein synthesis in zebrafish embryos. After validating KD efficiency, assessment of motor reactivity at different timepoints through touch- and light-evoked response analyses showed a significant delay of response and locomotor behaviour, respectively, in MO-injected embryos, reminiscent of the canonical psychomotor retardation and intellectual disability present in CdLS patients. Impairments in muscle development were excluded through birefringence microscopy. Our results suggest that Mau2 KD in zebrafish could represent a good model to study MAU2 role in CdLS insurgence. Future analyses will be focused on better characterize Mau2 KD phenotype, including craniofacial morphogenesis, and its rescue with human wildtype or pathological MAU2 variants.