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PRESS RELEASE (2024/10/16)

Zebrafish as a model for studying rare genetic disease
Researchers employ zebrafish to study the underlying mechanism of Nager syndrome

Fukuoka, Japan—Nager syndrome, or NS, is a rare genetic disease that affects the development of the face and limbs, usually causing anomalies in the bone structures of the jaws, cheeks, and hands. With a prevalence of less than 100 cases ever reported, not much is known about the disease except the fact that mutations in the *SF3B4* gene are its primary cause. Now, in a recent study made available online on September 15, 2024 and upcoming in the November issue of *International Journal of Biological Macromolecules*, researchers from Kyushu University have developed a convenient approach to explore the underlying mechanisms of this extremely rare disease.

When studying diseases or genes related to diseases, using animal models is often the best approach. The zebrafish is one such commonly used animal model. This is because many genetic disorders that affect mammals affect zebrafish in virtually the same way, allowing scientists to shed light into the nitty gritty of complex diseases.

In the present study, the researchers noted that the genetic and embryonic features of how the face and skull develop in zebrafish are similar to those in mammals. This, in turn, suggested that zebrafish could be used to model NS.

Accordingly, an international research team led by Associate Professor William Ka Fai Tse from Kyushu University's Faculty of Agriculture, genetically engineered zebrafish to carry a mutated *sf3b4* gene, resulting in a condition closely mirroring human NS. "Our group employed a zebrafish model to unfold the pathogenesis of this rare craniofacial disease. We aimed to identify molecules that play critical roles in the disease's development and progression, along with potential therapies to reduce its severity," explains Dr. Zulvikar Syambani Ulhaq, a JSPS Invitational Research Fellow at Kyushu University and the first author of the study.

Once the animal model was established, the team conducted an extensive series of experiments to compare mutated and non-mutated specimens.

After careful analyses of cellular stress, bone structure, and apoptosis, the researchers determined that *sf3b4*-deficient zebrafish have suppressed levels of the gene *fgf8*. This in turn affects the expression pattern of a type of cells called neural crest cells (NCCs). NCCs play an essential role during the early development of the facial structure, and their dysregulation could be strongly linked to the features of NS.

Moreover, the team found that apoptosis triggered by excessive oxidative stress was more prominently detected in *sf3b4*-deficient zebrafish, possibly contributing to the pathogenesis of NS. More importantly, injecting mutant zebrafish with human-derived FGF8 significantly reduced NS features, hinting at a potential therapeutic strategy for the disease.

Tse highlights the importance of conducting basic research in less explored diseases, since the little insights that we gather can make all the difference in the lives of those affected. He further explains, "Unlike cancer or diabetes, rare diseases like NS are not priority research objectives among pharmaceutical companies, and the small groups of patients suffering from them are

always overlooked. Our work sheds important light on this disease and can bring hope to those patients."

Tse's group welcomes collaborations and donations from various parties, from clinical doctors, patients, families to basic researchers. "If you agree with our concept and would like to contribute to the basic research in rare diseases, we encourage you to contact us," he says.

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For more information about this research, see "Fgf8 contributes to the pathogenesis of Nager syndrome", Zulvikar Syambani Ulhaq, May-Su You, Taijiro Yabe, Shinji Takada, Jen-Kun Chen, Yukiko Ogino, Yun-Jin Jiang, and William Ka Fai Tse, *International Journal of Biological Macromolecules*, https://doi.org/10.1016/j.ijbiomac.2024.135692.

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

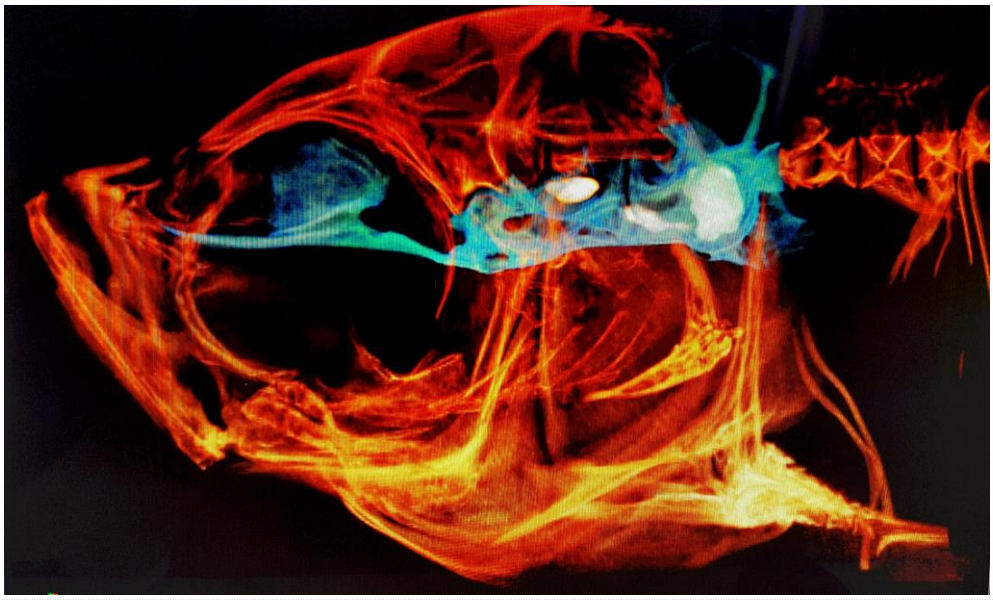

Fig. 1. Head bone structure of an adult zebrafish. Given that the developmental processes of zebrafish facial structure is similar to human, they can be leveraged as a low-cost and readily available animal model for exploring the underlying molecular mechanisms of craniofacial diseases. (William Ka Fai Tse/Kyushu University)

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