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Development of Diabetic Zebrafish Model for Genetic Screening

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Neonatal diabetes is a rare subset of the disease diabetes and affects an estimated 1 in 250,000 births. As in other types of diabetes mellitus, the body is unable to effectively control blood glucose levels due to a faulty insulin response. The ATP-sensitive potassium (K_{ATP}) channel is instrumental in insulin response, and gain of function mutations in its two subunits, kir6.2 and SUR1, are the primary cause of neonatal diabetes.

Previous studies have shown that the SUR1 subunit, which regulates channel sensitivity, can be targeted with the drug sulfonylurea as a form of treatment for the disease. However, required level of treatment and symptom severity of the studied cases can vary widely. This variation in expression of the mutations can be caused by many underlying factors, some of which may be mutations in other parts of the genome. A possible method to isolate these modifiers is a forward genetic screen.

To do so, we made an inducible neonatal diabetes model. We chose to use zebrafish as our model organism because of their similarities to humans and other practical advantages. We created a kir6.2 gain of function construct and established lines of fish that expressed the mutation. After testing, they have recapitulated several aspects of the disease in humans. In addition, a few assays essential for the screening process have been developed. With these tools, we will be able to identify individuals that deviate significantly in expression of the disease and genotype them to find candidate genes that modulate neonatal diabetes in humans as well. This will improve our understanding of the disease and inform future treatment.