# SEARCHING FOR GENES LINKED TO BIRTH DEFECTS

A range of techniques for EARLY TESTING AND TREATMENT OF EMBRYONIC DISORDERS is being developed by researchers at the biggest hospital in northern China.

**Neural tube defects (NTDs)** — flaws in the tube that develops into the brain and spine as the embryo develops — are the second most common birth defect following heart defects.

In northern China, nearly four out of 1,000 live births are affected by NTDs[1], linked to risk factors, including insufficient folic acid in a mother's diet, excessive alcohol consumption, pesticide and X-ray radiation exposure, and history of stillbirth. The NTD incidence is nearly four times the global average.

Geneticist and paediatrician, Zhengwei Yuan, has been conducting research at the Key Laboratory of Pediatric Congenital Anomalies of the Shengjing Hospital of China Medical University since 1996. Here his team has identified genes that may underpin NTDs, as well as developed new *in utero* tests and treatments.

"Our translational research projects range from embryo screening and interventions to postnatal assessment and rehabilitation," says Yuan.

**▲Geneticist Zhengwei Yuan (right) at the Shengjing Hospital of China Medical University, is striving to understand the development of embryos, as depicted in this artist's impression (left).**

## EMBRYONIC SCREENING

NTDs can lead to symptoms including leg paralysis, incontinence and conditions such as spina bifida and 'anencephaly', where parts of the brain and skull are missing. NTDs can be caused by both environmental and genetic factors, but often the precise cause of specific instances is elusive, he explains.

Yuan's team has identified several genetic factors in mice. Among these discoveries, was a link to abnormally high levels of nuclear factor I-C (NFIC) — a transcription factor that translates DNA into RNA. They also found that the high NFIC levels activate miR-200b, an RNA that helps regulate a gene called *Ambra1*, which regulates the breakdown of cells. This finding suggested a mechanism for the way NFIC triggers NTDs, and was published in 2022[2].

Yuan's team have launched a series of nationally funded projects, unravelling many other NTD-related genes and their molecular mechanisms in animal models through advanced multi-omics technologies, says Yuan.

But, so far, "only a few NTD-related genes identified in animal models have been confirmed in human cases," he cautions.

## DIAGNOSIS TO TREATMENT

His team is also working to make early embryonic diagnosis of NTDs and other congenital conditions a reality. At the moment, a NTD is diagnosed using ultrasound or amniocentesis, where a needle is used to remove small amounts of fluid from around the fetus.

From studies of human maternal serum, Yuan's team has identified 24 proteins and 20 RNAs that might be able to be used as non-invasive prenatal screening markers of NTDs and other congenital conditions[3]. "We have combined molecular markers and machine learning to test four early-warning models for congenital malformations," he says.

The team also wants to improve treatment of NTDs. Currently, treatment focuses mainly on tissue repair to fetal spinal tissue for life-threatening disorders, leaving the damaged nerves untreated. They are hoping to conduct preclinical studies of stem cell therapies to repair and reconstruct neurons before the birth, via microsurgery and microinjection.

Yuan's team also actively promotes exchanges with international academics and has worked to help write national guidelines summarizing their experiences of birth defect diagnosis.

On the research side, the laboratory plans to incorporate big data technologies in observational studies across the entire embryonic development period. "We are building more specialized patient cohorts on a larger scale, and initiating more randomized and controlled studies," says Yuan. ■

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