Scientists unlock cause of congenital birth defects

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By taking precautions during pregnancy, women can reduce the risk that their babies will have congenital defects. Credit: AAP/April Fonti

Australian scientists have discovered for the first time how nature and nurture combine to increase the risk for women of giving birth to a baby with congenital defects, according to a study published today.

Landmark research by scientists from Sydney's Victor Chang Cardiac Research Institute, published in the journal *Cell*, shows how the two factors interact to increase the severity and likelihood of birth defects, including abnormalities in the heart, kidneys, brain, limbs and cranio-facial regions (cleft palate).

The researchers demonstrate how hypoxia, or a period of low oxygen

during pregnancy, combined with a genetic risk factor of having only one functioning copy of a gene, increases tenfold the chance of giving birth to a baby with congenital scoliosis, a malformation of the spine that affects around 1 in 1000 people.

Professor Sally Dunwoodie, head of the Embryology Laboratory at the institute, Professor at the University of NSW and senior author on the study, said the findings brought scientists a step closer to understanding why some people in families developed diseases and others did not.

It also showed that mothers could adopt simple strategies to help prevent the defects occurring.

“This is the first time anyone in the world has shown that both nature and nurture, in combination, are molecularly responsible for causing many birth defects.

“This research is hugely exciting and will help us to genetically diagnose a whole range of birth defects, and give advice to women on how and when to avoid certain activities when pregnant. We hope it will eventually lead to the development of therapeutics to stop these defects occurring in the first place.”

Hypoxia during pregnancy can be caused by a range of circumstances, including poorly controlled sugar levels in diabetics, smoking, high altitude, prescription and recreational drug-use, anaemia or a poorly functioning placenta.

Professor Dunwoodie and her colleagues studied individuals with congenital scoliosis and found that having just one, instead of two functioning copies of a known gene from either the mother or father, was a major risk factor for causing the abnormal formation of vertebrae in embryonic development.

They then went on to test the genetic risk factor in mice, when combined with hypoxia. They found a marked increase in spinal abnormalities in the offspring when the mothers were exposed to only eight hours of low oxygen during a 21-day pregnancy.

Michael Davies, a senior research fellow and epidemiologist in the Discipline of Obstetrics and Gynaecology at the University of Adelaide, said oxygen conditions varied enormously as the human embryo moved through a series of developmental stages, from conception to postnatal development.

“Too much can be lethal if embryo culture conditions operate at high oxygen levels, while the converse is true in later pregnancy.

“Even postnatally, high oxygen immediately after birth can cause blindness. Mechanistically, there are a number of genes regulating growth and vascular development that respond to oxygen conditions for their expression.

“The implications [of this research] are great, but we also need to consider a complex set of maternal and fetal adaptations to changes to demand both across pregnancy and acute challenges, like walking up a flight of stairs.”

Associate Professor Davies said there was no apparent epidemic of birth defects in the babies of women who played sports while pregnant, so the effects of oxygen deprivation in humans might be subtle or specific.

“Living at altitude does not cause problems as the placenta grows larger to compensate, but acute challenges or exposures to chemicals such as carbon monoxide would be interesting to study.”

Richard Cotton, a Professor of Genomics at the University of

Melbourne, described the findings as “novel and hugely exciting”. “This study examines a disease and finds both the insult and the genetic fault required in one report. It will stimulate work in other diseases. For example, looking directly for genes that are faulty in affected cases.

“Regarding prevention, clinicians may develop recommendations based on this work analogous to those for alcohol consumption, which is another environmental insult [like hypoxia], causing malformation.”

Professor Bob Graham, Executive Director of the Victor Chang Cardiac Research Institute, said: “It may not necessarily be a lack of oxygen that allows the underlying gene defect to be revealed, it could be a lot of other environmental factors, such as anaemia or lack of folate. But the message is, if you have family history of disease or you know you have a defective gene, mums need to be extra careful during pregnancy.”